RECOMBINANT DNA RESEARCH
Volume 3

Documents Relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules" November 1977 - September 1978

Appendices

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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RECOMBINANT DNA RESEARCH

Volume 3

Documents Relating to
"NIH Guidelines for Research
Involving Recombinant DNA Molecules"
November 1978—September 1978

APPENDICES

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Prepared by the
Office of the Director, NIH

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APPENDIX A

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APPENDIX A

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RICHARD M. HARTZMAN
ATTORNEY AT LAW
281 WEST 87TH STREET
SUITE 52
NEW YORK, NEW YORK 10024
212 - 666-8146

September 30, 1977

Dr. Donald S. Frederickson
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I am writing to you on behalf of Friends of the Earth in regard to the proposed revised NIH guidelines for recombinant DNA research.

We are deeply disturbed that these revisions have been proposed and published in the Federal Register for comment without the NIH having prepared the legally required environmental impact statement. The National Environmental Policy Act requires that an environmental impact statement "shall accompany the proposal through the existing agency review processes". Adequate public disclosure of the information base and analysis of the environmental impacts of the proposed revisions is not possible without a detailed impact statement, and hence informed and effective public comment is precluded. Nor can there be any assurance that the issues have been thoroughly considered and that the decisions being made are rationally based. The NIH action proposing revised guidelines is a continuation of the scientifically and legally defective processes used with respect to the entire recombinant DNA program and the promulgation of the original guidelines. If the NIH does not take immediate steps to comply fully with the law, Friends of the Earth will be constrained to initiate further legal action.

In addition, we find the 30-day comment period for the revisions wholly inadequate. Not only are the guidelines themselves highly complex, but the proposed revisions are profuse and often subtle. Nor would most interested commentators be able to obtain needed information concerning the basis for the revisions before the 30-day period had expired. A 60-day period for comment is much more reasonable for a complex matter such as this. In any case, the proposed revisions should be withheld from further consideration until an environmental impact statement has been prepared.

Finally, we are of the opinion that public hearings should be held before any final decisions are made on revisions to the guidelines. Merely holding open meetings of NIH advisory committees is not sufficient. This has been an issue of great public concern that has involved city councils and town meetings, state agencies and legislatures, federal agencies (such as the Environmental Protection Agency), and the United States Congress. It would be a serious omission if the key mechanism safeguarding recombinant DNA research, the NIH

guidelines, were revised without public hearings that include an opportunity for interested groups and individuals to participate.

We are confident that, in the spirit of good government and concern for public health and the environment, you will take the necessary steps to comply with the law.

We await your prompt response.

Thank you.

Sincerely,

Richard M. Hartzman

Richard M. Hartzman

jc

cc: Edward Kennedy
Paul Rogers
Joseph Califano
William Cartland
George Wald
Jonathan King
Philip Boffey
Nicholas Wade
Colin Norman

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OFFICE OF ENVIRONMENTAL HEALTH AND SAFETY

SAN FRANCISCO, CALIFORNIA 94122

October 11, 1977

Dr. William J. Gartland, Jr.
Executive Secretary
Recombinant DNA Molecule Program
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Gartland:

In response to your request for comments on the proposed revised "Guidelines for Research Involving Recombinant DNA Molecules", I would like to comment as follows:

1. Autoclaves - It appears there is a relaxation of this requirement for P-3 facilities. I believe that in the current guidelines an autoclave was required within the controlled area - now it appears to be required only within the building (Ref.: page II-17(6)).

   Since there are more stringent requirements as you move from P-1 to P-4 facilities, i.e., P-1 - no autoclave required, P-2 - autoclave within the building, to P-4 - double ended autoclave with interlocks, it would seem logical that an autoclave be available within the controlled area of a P-3 facility.

2. Page II-19 (P-4 level - "Eating, drinking...") - I believe the asterisk should be omitted, since this same requirement applies to P-1 to P-3 also.

3. I note the number of appendices have been reduced. I found the former appendix "D" especially valuable in providing detailed procedures.

In general, I have found the proposed revision a great improvement over the current Guidelines. Congratulations.

Thank you for the opportunity to review and comment.

Sincerely,

Frank A. Gohr, Dr. P.H.
Biosafety Officer

FAG/ew

The Joseph and Rose Kennedy
Institute for the Study
of Human Reproduction
and Bioethics

Georgetown University
Washington, D.C.
20057
202/625-2371

October 11, 1977

Donald S. Frederickson, M.D.
Director, National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

Thank you for sending a copy of the proposed revisions of the NIH Guidelines on Recombinant DNA Research, as published in the Federal Register on Tuesday, September 27, 1977.

I note that in the introduction to the revised Guidelines, you mention a December 1977 Director's Advisory Committee meeting, at which all comments on the proposed revisions will be discussed. The introduction leaves open the question whether, as in February of 1976, the Director's Advisory Committee will be augmented by the appointment of additional ad hoc members and whether there will be an opportunity for oral public comment at the December meeting.

I write to urge that representatives of contrasting points of view be included to the greatest feasible extent at the December meeting. There are three reasons for my making this recommendation.

First, the breadth of representation at the February 1976 Director's Advisory Committee was perhaps the decisive factor in establishing the legitimacy of the initial set of NIH Guidelines on Recombinant DNA Research released in June of last year.

Second, until now members of the public and critics of recombinant DNA research have not been invited to comment on proposed revisions of the Guidelines; indeed many well-informed persons have probably been unaware that the revision-process was in progress. To them, the chance to submit written comments within a maximum of 60 days may seem like an inadequate opportunity to participate in a policymaking process of great national and international significance.

Third, a review in December which includes public hearings may have the important benefit of encouraging thoroughgoing, constructive criticism of the revised Guidelines and is unlikely to produce sensationalistic fallout. I base this rather sanguine judgment on our experience at the February 1976 meeting (at which a large audience followed a technical discussion intently) and on the experience of the National Commission, which has held lively but instructive public hearings on such volatile topics as fetal research and psychosurgery.

Thank you for making the proposed revisions so widely available through publishing them in the Federal Register. Best wishes in your planning for the December Director's Advisory Committee meeting.

Sincerely yours,

LeRoy Walters, Ph.D.
Member, NIH Recombinant DNA Molecule
Advisory Committee

LW:lt

cc: Dr. DeWitt Stetten
Dr. Joseph Perpich
Dr. William Gartland

ROCHE INSTITUTE OF MOLECULAR BIOLOGY

NUTLEY, NEW JERSEY 07110

October 13, 1977

Dr. Donald S. Frederickson
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Md. 20014

Dear Dr. Frederickson:

I am writing in response to your request for comments on the proposed revised Guidelines for Recombinant DNA research, published in the Federal Register, volume 42, number 187, September 27, 1977.

Since I have been involved in Recombinant DNA issues in various capacities for some time, I have followed the recent developments in this area with considerable interest. Especially noteworthy has been the growing consensus, based on accumulated experience and risk-assessment experiments, that Recombinant DNA research utilizing E. coli K-12 based systems poses no significant risk to the public health and environment. This consensus deserves emphasis because it was in fact, concern for the public welfare that seemed to distinguish this area from other types of biomedical research, and was the major justification for the establishment of special guidelines. It appears that the NIH Guidelines' reliance on the E. coli K-12 based-systems was well founded, and biological containment will work even better than some of us had expected.

It is, of course, essential that the revised Guidelines reflect changes in the state of our knowledge concerning the efficacy of various containment procedures and conditions. Many of the revisions, including most of the "containment guidelines for permissible experiments" do seem to reflect these changes. However, in a few instances, there are inconsistencies and it is two such instances that I address below:

1. The experimental Guidelines for "viruses of plants" (page 49602) specify P2 + EK2 or P3 + EK1. Since the two types of containment are complementary, the flexibility provided by balancing changes in physical containment with changes in biological containment is certainly reasonable. From the standpoint of the experimenter, such flexibility is also most desirable,

continued . . . . . .

since many more types of experiments are possible using EK1 vectors. The inconsistency I see is the failure to provide a similar flexibility for other P2 + EK2 experiments, for example, shotgun experiments with DNA from mammals other than primates, or from birds (page 49601).

2. There is little use in designating experimental guidelines for "permissible experiments" which cannot practically be met. This is the case for the classification "DNA viruses and DNA transcripts of retrovirus genomes". Furthermore, the designation of containment for this class of experiments seems disproportionately conservative on several counts:

(a) Viruses in this class belong to the NCI category called "low-risk". In their naturally infectious forms, such viruses can be handled at what would correspond to a P2 level of containment. If we accept the Guidelines' conservative approach of assigning recombinant organisms to levels "not less than that required for handling the most hazardous components", then a reasonable level for these experiments might be P3. Instead, they have been placed at the unobtainable level of P4 (+EK1). To compound the problem, essentially no flexibility has been provided, for in this particular instance, a decrease of one step in physical containment (P4 → P3) requires an increase of two steps in biological containment (EK1 → EK3). This requirement again puts the experiments in the realm of the unobtainable, since no EK3 vectors are yet available (or even in the testing stage).

(b) What is the special concern for this category? As far as I can tell, it relates to a scenario in which DNA of an animal tumor virus is presented to a cell (presumably via E. coli K12 infection of the gut) in a form for which it has no natural resistance. Since it already seems clear that the E. coli K12 carrying a DNA insert cannot become an epidemic pathogen (especially if it is an EK2 strain) the only potential hazard is to the investigator and not to the public. Therefore, the basis for special concern and conservatism in this versus other types of viral research seems to have disappeared.

(c) How real is the hazard to the investigator? We already have some data from preliminary experiments of Martin and Rowe which bear directly on this point. Using the model system of polyoma virus and its highly susceptible mouse host, they showed that naked polyoma virus DNA could

continued . . . . . .

indeed cause viral infection of mice and the highest infectivity was observed after subcutaneous injection. Impressive as this fact seems, this infectivity is still only 5×10^{-5} of the specific infectivity of the virus in its native form. One interpretation of these data is that preparing naked DNA is quite an effective method of attenuating this virus. Thus, research with DNA, or recombinant DNA including these viral genes, seems to provide an important safety advantage--at least in this particular virus-sensitive host system. It seems probable that such research would provide an even greater safety advantage when dealing with this and other viruses in a virus-insensitive host system (i.e. the hypothetical situation in which an investigator somehow becomes infected with an E. coli K12 containing viral genes).

(d) The viruses in this category are not human pathogens, and they represent animal model systems which are of great biomedical importance. The current practical moratorium on recombinant DNA research with these systems does not seem to be a sound balance of benefit versus risk.

I hope that these comments will be helpful to you and that they will encourage the Recombinant DNA Advisory Committee to reconsider some of the revised classifications.

Yours truly,

A. M. Skalka, Ph.D.
Department of Cell Biology

AMS:pcp

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOCHEMISTRY

PAUL BERG
Willson Professor of Biochemistry

October 13, 1977

Dr. Donald Fredrickson
Director
National Institutes of Health
5333 Westbard Avenue
Bethesda, Maryland

Dear Don,

I am writing in response to your call for comments on the draft version of the Revised NIH Guidelines for Recombinant DNA Research.

First, let me say that I am delighted that the earlier commitment to review and modify the Guidelines in the light of more current assessments of risks has moved ahead so expeditiously. In only that way will we be able to prevent the accumulation and perpetuation of unreasonable requirements.

There are two recommendations in the draft version with which I would like to take issue:

1) The Introduction argues for defining recombinant DNAs as to whether or not they are novel, defining novel as "those molecules consisting of segments of any DNA from different species that are not known to exchange DNA by natural physiological processes". "In general", the Introduction goes on, "recombinant DNA molecules formed from any combination of DNAs will not be considered novel when all the components are derived from genomes known to replicate within the organism used to propagate the recombinant DNA." After that clear and definitive enough judgement why is the Director of the NIH asked to prepare a list of those combinations of DNAs (viral, extrachromosomal or chromosomal) that are <u>not</u> considered novel and, therefore, to be excluded from coverage by these Guidelines. It seems more logical that the Director should prepare a list of those combinations which, he views as novel in spite of the fact that, according to the definition, they are not! Isn't it administratively simpler to be explicit about the exceptions rather than to try to enumerate all possible combinations that fit the definition? Also, wouldn't it be easier to eliminate the exceptions rather than make additions, as new evidence becomes available?

So much for the wording, - now for substantive issues. What is the scientific justification for insisting that recombinants between polyoma and mouse DNA or beteween SV40 and monkey DNA are more novel than recombinants between DNA from E. coli and λ phage or plasmids? There is un-

equivocal evidence that polyoma-mouse DNA recombinants arise naturally in the laboratory and very likely in the wild. Most probably the same is true for SV40 and the DNA of its host cells. Both types of recombinants have been in virus stocks for years and may already have infected innumerable people and animals. Moreover, such naturally-arising recombinants are presently being studied in several laboratories in this country and abroad using routine containment. Consequently, I see no justification, other than political considerations, for restricting the construction of these viral-host DNA recombinants in vitro. Perhaps politics is an overriding factor but then we ought to be explicit about saying so.

2) The draft revision of the Guidelines calls for P2-EK2 containment for shotgun experiments with mammalian DNA. It is not clear as to whether the same recommendation is made for attempts to clone integrated polyoma or SV40 DNA sequences from non-primate mammalian DNA in E. coli. I note that page III (9g) focuses on cloning integrated retrovirus nucleotide sequences from mammalian cell DNA but says nothing about nucleotide sequences of integrated DNA viruses. Is it intended that such experiments be done only under the containment stated on page III-9 (1) (a), i.e. P4-EK1 or P3-EK3? As I read this text it says that shotgun experiments with mouse DNA can be done in E. coli using P2-EK2 if one is looking for the hemoglobin or HGPRT gene but if one is seeking a viral sequence from the same pool the it must be done in P4 or P3-EK3 (or in effect it is now forbidden). Can it be inferred from this that experiments directed to isolating polyoma or SV40 DNA segments is far more dangerous than the possibility of cloning an unknown cryptic viral sequence? My own view is that the entire question of what containment is appropriate for cloning animal virus DNAs, free and integrated, in pro- and eukaryote vector-host systems needs to be reexamined. I would urge you to convene an appropriate group of experts to make recommendation on this matter for the next cycle of revisions in the Guidelines.

There is one other aspect of the proposed revisions that I'd like to comment upon. On p. IV-9, where the responsibilities of NIH staff are outlined, I read that "no grants or contracts (and presumably fellowships) are awarded for recombinant DNA research unless (a)..., (b) have been properly reviewed and recommended for approval and (c) include a properly executed M.U.A.;... I interpret that to mean that awarding, and not the consideration of the grant, contract or fellowship application, is contingent upon the submission of an M.U.A. At present, before a fellowship proposal can be reviewed by an NIH committee there must be an M.U.A. on file. This requirement has created an additional burden on the investigator and the institutional review committees. Very often the investigator already has M.U.A.s and approved facilities for the work being proposed. But now a new M.U.A. must be sought and authorized, etc. etc., even if the applicant doesn't get the fellowship or doesn't do that project. As I interpret the new version it seems much more reasonable and accomplishes the same purpose: No fellowship research can be undertaken without an M.U.A. Perhaps it would be sufficient to have the fellowship application show that the preceptor has facilities required for the work but the formal M.U.A. would be needed prior to activation of the fellowship.

The revised version of the Guidelines is a step in the right direction. I still believe that they are overly restrictive but they do permit a good deal of the work to proceed, albeit slowly. I hope that the administrative mechanisms at your end and ours can be further improved so that the review and negotiations are not so protracted.

With warm regards,

Sincerely yours,

Paul

PB:ab

THE MILTON S. HERSHEY MEDICAL CENTER
THE PENNSYLVANIA STATE UNIVERSITY

DEPARTMENT OF MICROBIOLOGY
HERSHEY, PENNSYLVANIA 17033
717 534-8253

October 17, 1977

Donald S. Fredrickson, M.D.
Director
Department of Health, Education and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I respond to your note dated October 8, 1977 with the attached draft of revised guidelines for recombinant DNA research. In general, I find the draft an excellent one but wish to make the following comments:

1. Safety is still based primarily on containment. Though training in aseptic technique is mentioned, this is clearly not the focus of the guidelines. Yet it probably represents the key to safety. How will this be evaluated? Containment facilities can be checked but no provision is made to determine the level of training of the principal investigator and his personnel (it may be as important to train the janitor and glassware washer as the scientist). Any "break" in technique will destroy physical containment procedures.

2. In V. Footnotes (49605) under number 5 (paragraph 2), it is categorically stated that "genes coding for the synthesis of virus capsid components have not been associated with oncogenesis". This is true for the adenoviruses and papovaviruses. It is <u>not correct</u> for the herpesviruses. Cells transformed by Epstein-Barr, herpes simplex and cytomegaloviruses contain genes for structural proteins. The "early" regions of herpesvirus DNA code for structural proteins. Thus, proteins found at the membrane of transformed cells contain virus structural components.

3. Amazingly, appendix B makes no reference to herpes simplex or cytomegalovirus presumably because these viruses have not yet been shown

to cause tumors in experimental animals. However, they transform cells (including human cells) to malignancy in vitro and have been associated with human neoplasias by a variety of indirect tests.

I hope these comments are of some value to you.

Sincerely,

Fred Rapp, Ph.D.
Professor and Chairman

FR/nk

2677 Ellendale Place
Los Angeles, California 90007
(213) 733-9307

October 17, 1977

Donald S. Fredrickson, M.D., Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

My comments on the proposed revised Recombinant DNA Research Guidelines (Federal Register 42, #187, September 27, 1977, pp. 49596-49609) are these:

1) I note with favor that the list of unfundable "forbidden" experiments (p. 49601) is virtually identical with the 1976 list (FR, July 7, 1976, pp. 27914-27915). Full retention of this set of proscriptions realistically recognizes the continuing imperfectness of both physical and biological containment.

2) However, I must advise once again that funding guidelines are inherently inadequate to cope with the potential biohazards of recombinant DNA research. The Guidelines consist in essence of a series of recommendations for containment levels. They reflect the assumption that relatively harmful genes can be accurately classified by their organismic source, and thus assigned to confinement sufficient to prevent escape and establishment beyond the laboratory. Recent research on the process of transcription has vitiated the assumption of basically linear relationship between gene and gene product. The Guidelines admit that the term "free of harmful genes" is "unavoidably vague" (p. 49605). Research since promulgation of earlier versions of the Guidelines has changed "unavoidably" to "enormously". An extremely brief summary of this work would include these points:

It has been found that bacterial genes may sometimes jump from place to place on DNA molecules (Science, 30 July 1976, p. 392). Moreover, gene sequences sometimes overlap, and occasionally may be completely nested within a different gene's DNA sequence (Science, 10 June 1977, p. 1187). Furthermore, "spliced" messenger RNA has been found which is transcribed from three separated areas of a viral DNA molecule (Science News, July 30, 1977, p. 70). In addition, "action at a distance" has been discovered--a protein bound to DNA at one spot can affect gene expression at a position some distance away (Science, 7 October 1977, p. 41). Cumulatively, these findings indicate that genes cannot be conceptualized as simple uninterrupted and stable nucleotide sequences. It follows then, since unknown idiosyncrasies in transcription are crucial, that we cannot confidently prevent the formation of harmful gene products, or their escape, by matching various source (donor) DNAs with various containment procedures.

3) Nor can assurance be drawn from the apparent absence of adverse health effects in recombination experimentation to date, for these reasons: (A) Recombinants potentially harmful to important target species may have already been created, but may simply not have been viably carried to those species. (B) Recombinants potentially harmful to man may have gone unnoticed thus far due to the fortunate good health, immunological history, or inherited resistance of the laboratory personnel exposed to them. (C) Harmful recombinant genes transferred to viable

microbial strains may have slow-acting noxious effects (e.g., elaboration of carcinogens or cumulative toxins) which have thus far escaped detection. (D) As molecular biology proceeds, it will become possible to create many complex recombinants not producible today. Hence, even were it established that present-day techniques pose no hazard, advancing technology may at any time achieve the creation of a virulent and uncontrollable microorganism.

4) No government agency has yet issued an environmental impact statement on the widespread application of recombinant DNA technology (as distinct from the brief draft EIS by NIH on the impact of the Guidelines, issued August 19, 1976). The just-announced legal ruling that the Upjohn company will be permitted to patent its novel form of Streptomyces sets a precedent which portends legal and commercial anarchy. In the absence of comprehensive environmental-impact review, and with the profit incentive inherent in patent rights, and unfettered even by the provisions of the Guidelines, private industry may be expected to kill and injure humans with self-distributing, self-maintaining biological pollutants as it has with radioisotopes and organic chemicals.

5) The proposed revised Guidelines totally disregard any requirement for health insurance for laboratory personnel, or liability insurance to indemnify the public (see the section, "Roles and Responsibilities," p. 49604). Such omissions could be logically justified only on the assumption that no biohazard was involved in DNA recombination work, in which case the Guidelines would be unnecessary. Given Litton Bionetics' inability to obtain insurance coverage for its prospective PL4 NIH contract work at Fort Detrick, and its resultant withdrawal from that research, it is incumbent on the federal government to deal decisively with the matter of insurance. A very serious neglect of public trust in involved in the government's continuing refusal to address the issue.

6) The proposed revised Guidelines, like their predecessors, do not even attempt to deal with human malfeasance in any of its pertinent manifestations. These include use of unauthorized vectors (Science, 30 September 1977, p. 1342), quasi-deliberate release to the environment through calculated negligence regarding containment, theft from laboratories or during transportation, sabotage resulting in loss of containment, and malevolent attempts to create or distribute noxious novel organisms. It has been said, by way of dismissing this topic, that inventor Henry Ford should not be held accountable for the adverse consequences of the automotive industry--smog, military tanks, and 45,000 American motor vehicle fatalities per year. But to properly complete the analogy, if adequate foresight and control could have been applied early in the history of the automobile, millions of lives could have been saved through the use of acceptable safety measures. Again, if the budding nuclear industry had early recognized the burden of security and safeguards which would eventually be found necessary to its functioning, past and future history might be quite different.

7) The proposed revised Guidelines do not refer to pursuit of international agreements, achievement of which was deemed "essential" in your introduction to the 1976 Guidelines (FR, July 7, 1976, p. 27905).

Forceful representations to Congress are necessary to safeguard public health and to preserve your estimable professional reputation. Federal monopoly is the logical institutional model to pursue.

L. Douglas DeNike

Enclosure: Curtiss letter critique

L. Douglas DeNike, Ph.D.

August 11, 1977

TO: Coalition for Responsible Genetic Research

FROM: L. Douglas DeNike, Ph.D., 2677 Ellendale Place,
Los Angeles, CA 90007 (213) 733-9307

RE: Deflating the Curtiss letter

A widely-circulated 13-page letter has recently had a "big impact" in support of the idea that recombinant-DNA hazards have been overestimated (Science, 22 July 1977, p. 348). The letter was written April 12 by Roy Curtiss III of the University of Alabama, Birmingham, to NIH Director Donald S. Fredrickson. Its author by no means asserts that recombinant DNA work is free of biohazards. He merely argues that standard "EK1" microbial strains are sufficiently safe if all other precautions are observed. Since erroneous secondhand interpretations of Curtiss's views may weaken pending Congressional legislation, or its subsequent enforcement, this memorandum of clarification is offered.

Here is Curtiss's main conclusion (letter, p. 9): "In view of all the accumulating information discussed above (without any literature references!), I have gradually come to the realization that the introduction of foreign DNA sequences into EK1 and EK2 host-vectors offers no danger whatsoever to any human being with the exception already mentioned that an extremely careless worker might under unique situations cause harm to him- or herself." He does not intend to offer any general assurances regarding conjugative plasmids in wild-type E. coli, or wild-type phage, or anything beyond.

Curtiss and his colleagues labored for many months to develop the less-viable EK2 "χ1776" (chi 1776) E. coli strain to provide an additional safety factor in recombinant DNA experiments. But χ1776 is described as "...a very poor grower, is inconvenient to use, and requires constant monitoring to verify its many biological properties" (R. Novick, Bulletin of the Atomic Scientists, May 1977, p. 20). By implication, Curtiss argues that the field need not be saddled with the inconvenience of χ1776 or other specially crippled bugs.

However, Curtiss ends up supporting legislation to make the NIH safety Guidelines ("or some slight modification thereof") mandatory for all individuals using recombinant DNA molecules for whatever purpose, whether in the public or private sector (letter, p. 12). In short, he acknowledges genuine risks. For instance, on p. 11 he says it would be "rather stupid and unlikely" for research with wild E. coli and other enteric pathogens to be done in the same lab used for recombinant DNA work.

Since he recognizes that here may be real dangers, it is puzzling that Curtiss opposes licensing of laboratories and/or scientists, and opposes inspections save for P4 facilities (letter, p. 12). He wants to leave the policing largely up to "hard-working and conscientious" institutional biohazards committees--but he presents no evidence that such committees will in fact adequately watch over their peers. This, of course, reflects the fact that no experimentation has ever been done to test empirically the real-life efficacy of the biohazards-committee system in supervising recombinant DNA-safety standards. Despite the obvious need and the hundreds of scientists involved in the field, not one has sought to find out just how well local in-house overseers detect and correct deficiencies in prescribed equipment, materials, and procedures. This gaping hole in the "scientific" armor of the research gives the citizen little reason to feel confident. The experience of microbiology isn't terribly relevant since different hazards and training standards are involved. ⟶

Those who indiscriminately scatter seeds of unknown nature must presumably bear with whatever weeds spring up as a result. No one can guess the specific consequences as recombinant DNA techniques proliferate worldwide, and as the capabilities of gene-splicing practitioners (for good or ill) become steadily more powerful with the accumulation of new knowledge. Curtiss chooses to ignore the proliferation and puissance issues altogether. He notes that "...enteric diseases are very well controlled in the United States (emphasis added) by sanitary engineering..." (p. 6). This is reminiscent of Wallace Rowe's comment, "Developed (emphasis added) countries know how to prevent epidemics of enteric bacteria..." (Bulletin of the Atomic Scientists, May, p. 15). Those who wonder who will fill the moral vacuum regarding international agreements (deemed "essential" in the Guidelines) marvel at such parochialism.

The much-touted Guidelines are relatively meaningless if potentially harmful DNA cannot be accurately recognized in advance. Donor DNA may be adventitiously contaminated with that from deadly bacilli or other tag-alongs. In addition, recent research has largely destroyed the meaningfulness of the "harmful sequence" concept. It has been found that bacterial genes may jump from place to place on DNA molecules (Science, 30 July 1976, p. 392). Moreover, we now know that gene sequences sometimes overlap, and occasionally are completely nested within a different gene's DNA sequence (Science, 10 June 1977, p. 1187). Furthermore, "spliced" viral messenger RNA has been found which is composed from three separated areas on the viral DNA molecule (Science News, 30 July 1977, p. 70). Thus the potential hazard of any given DNA sequence will depend in complex fashion on idiosyncrasies in the host's translation processes, and on epidemiological and potentiating factors completely outside of the microorganisms under study--and beyond the training of the investigator. It may depend on the relative ability of possible victim organisms to generate antibodies, or on the likelihood that mutagenic chemicals or ionizing radiation may liberate a pathogenic subsequence by breaking a DNA chain at a key point. So much for the scientific foundation of the NIH Guidelines. Systematic basic safety research is almost completely lacking, and it may well be too dangerous to conduct many obvious risk-assessment studies until containment technology is improved; such is the plain meaning of the experiments ruled impermissible by the Guidelines. We know enough to say that certain organisms and procedures are especially likely to yield harmful consequences; we don't know enough to say that others are harmless.

Pontius Pilate committed a heinous deed by washing his hands. If recombinant DNA practitioners seem determined to follow in the same tradition, what can citizens do? They can insist on pinning full financial liability (without regard to fault) on any scientist or institution which generates an injurious recombinant. Curtiss's attitude shows clearly on p. 13, where he says, "The worst possible provision (for Congressional legislation) would be a stipulation of specific liability. This would act as a de facto prohibition of recombinant DNA activities in this country, the consequences of which would be staggering." In other words, after twelve pages of detailed argument, Curtiss says in effect that the scientists, their institutions, and the insurance companies still aren't willing to risk their financial skins. What he means is, "Don't ask us scientists to put our money where our mouth is. Don't require us to shoulder our logical insurance responsibility. Instead, let's all jump off the pier together--investigators and the public alike--and hope that we catch valuable fish instead of just drowning." It is heartening that Litton Bionetics, Inc. was forced to withdraw from NIH-contracted P4 recombinant-DNA experiments proposed for Fort Detrick, because of an inability to gain insurance coverage (Frederick Post, June 14, 1977).

* * *

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

CENTER FOR CANCER RESEARCH

77 MASSACHUSETTS AVENUE, CAMBRIDGE, MASSACHUSETTS 02139

October 18, 1977

Dr. Donald S. Frederickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don,

I appreciated receiving a copy of the proposed revised NIH Guidelines on Recombinant DNA research.

I want to strongly support the conclusion of the Recombinant Advisory Committee that "everything they have learned tends to diminish our estimate of the risk associated with recombinant DNA in E. coli K-12." I also support their conclusion that this does not mean we should drop our guard entirely but that we should begin the process of reducing the required containment levels for recombinant DNA research commensurately to our reduced estimate of risks. I would hope that with further experience with recombinant DNA research and further studies of bacterial pathogenesis, assessments of possible risks will continue to decline and that the containment requirements of the Guidelines will also continue to be relaxed.

One important step forward is the reduction of physical containment level for shot gun experiments in mammals. It has always been my belief that the major potential hazard from such experiments would lie in the accidental incorporation of endogenous viral nucleic acid into bacteria. The risk associated with such an occurrence now seems marginal and EK2 containment seems totally sufficient to prevent any conceivable hazard.

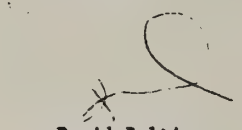
I believe you should be aware that the field of retrovirus research has been seriously hampered by the present NIH Guidelines. The availability of clones containing fragments of retroviral genomes would have advanced the field enormously already and are still badly needed. I, of course, recognize that clones containing retroviral DNA may present special concerns and I'm not suggesting that they should be made at will. With the present non-existence of P4 con-

tainment facilities, however, and without any certified EK3 vector, no possible work can go forward. I hope that you will consider the possibility of reducing further the containment requirements so that clones can be made using P3 plus EK2 if incomplete genomes are to be ligated into a plasmid. Except for Rous sarcoma virus, and possibly other sarcoma viruses, there is at present no reason to believe that one portion of the genome or another is reponsible for neoplastic transformation. Therefore, for non-sarcoma viruses, all fragments would fit the definition of containing "less than the complete potentially infectious viral genome" and would also not contain "any portion of the viral genome region that is known or suspected to be responsible for neoplastic transformation."

Finally, the rules of "DNA transcripts for other RNA virus genomes" for mammals are a bit odd. It is true that segmented genomes would be harder to make as complete DNAs than non-segmented genomes but it is difficult to imagine that a reverse transcript of a lytic RNA virus could be hazardous under any condition. This is doubly true if vaccine strains of viruses were to be used--after all these were selected to be safe for the human population and are given in large quantities to people.

Although I have suggested specific areas in which I believe that containment conditions could be altered, I want to support strongly the general tenor of the proposed revised Guidelines. I hope that you will find it possible to issue these as revised Guidelines in the near future.

Sincerely,



DB/mts

David Baltimore

BRANDEIS UNIVERSITY
WALTHAM, MASSACHUSETTS 02154

ROSENSTIEL BASIC MEDICAL
SCIENCES RESEARCH CENTER
617-647-2433

October 18, 1977

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

On October 5th through 8th the 7th International Conference on Spores was held. This is probably the largest meeting in which experts dealing with Bacillus subtilis come together to discuss their research and to develop future programming.

For the first time the isolation of the spore gene was reported at this meeting of international scientists and the concern over the difficulties in carrying out cloning experiments in this country was addressed. In response to that problem the following letter and signatures of experts in this field from a number of countries is attached.

We hope the opportunity for altering the NIH Guidelines permitting cloning of Bacillus genes in Bacillus will be permitted to enable this important research to go forward.

Sincerely yours,

H O Halvorson

Harlyn O. Halvorson, Director
Rosenstiel Basic Medical
Sciences Research Center

HOH/pmb

enc.

10/7/77

To: Dr. Donald Fredrickson
Director, National Institutes of Health, Bethesda, MD

As active workers in Bacillus microbiology, we strongly support the requests of a number of investigators to use Bacillus subtilis for DNA recombinant studies. The development of cloning technology with this species will be of great value for genetic investigations of a number of processes that cannot be studied in Escherichia coli: Specifically, this organism undergoes a simple developmental cycle and a genetic study of the process will allow conclusions applicable to higher forms of differentiation. At this time the genetics of this organism is hampered by the lack of a suitable system for complementation and dominance analysis. The construction of extra chromosomal elements is possible with DNA recombinant technology using natural plasmids for this species.

B. subtilis is a soil organism lacking known toxins for man, animals, and plants. A related strain, B. natto, is consumed in large quantities as a component of soybean cakes without causing infections. Nevertheless, there are reports of human infection involving B. subtilis. We do not believe that these rare incidents indicate that B. subtilis is pathogenic. Compromised hosts can be invaded by any microorganism and B. subtilis is no exception. B. subtilis is highly aerobic and very sensitive to several components of normal human serum. It is an unlikely candidate for human infections. Furthermore, it is highly sensitive to most commonly used antibiotics and can therefore be readily controlled.

The ability to form spores is characteristic and as such would

permit long term survival. We propose that in instances where the NIH guidelines require safer host systems that spore-defective mutants be employed. A strain equivalent to the EK-2 of E. coli K12 could be readily constructed that would have little or no survival outside of special laboratory environments.

We strongly urge that P-1 conditions be permitted for using B. subtilis to clone genes from prokaryotes that normally exchange genetic information. We as dedicated investigators in this field do not believe that this technology in Bacillus subtilis is hazardous to humans, animals, or plants.

Participants in the 7th International
Spores Conference
Madison, Wisconsin
October 5-8, 1977

Duke University Medical Center
DURHAM, NORTH CAROLINA
27710

OFFICE OF DIRECTOR
GRANTS, CONTRACTS AND SPECIAL PROJECTS

P. O. BOX 2891
TELEPHONE (919) 684-3178

19 October 1977

Dr. William J. Gartland
Executive Secretary
Office of Recombinant DNA Activities
Building 31, Room 4A52
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Gartland:

This letter, on behalf of the Duke University Biohazards Committee, is in response to your request for comments on the proposed revisions of the Guidelines for Research Involving Recombinant DNA Molecules.

It is hard to reconcile sentence 2 of the introduction defining recombinant DNA with Section III-B.1.a.(2) in which containment levels for intra-species recombinant experiments are discussed. In particular, the term "novel recombinant DNA" as cited in the introduction is ambiguous. If we assume that the guidelines apply to E. coli X E. coli cloning experiments, then the minimal containment level of P2EK1 or P1EK2 are unjustified, and allowing the Institutional Biohazard Committee to downgrade containment is going to introduce further confusion into the interpretation of the guidelines. We therefore propose that all experiments involving cloning of DNA fragments isolated from the chromosome of E. coli K12F, or one of its well characterized viruses or non-conjugative plasmatids utilizing approved EK1 vector systems, be subject to containment at the level of P1. It is our feeling that this covers the majority of cloning experiments now is progress and would simplify interpretation of the guidelines if this were explicitly stated.

Another area of concern to our committee is the disposition of MUAs submitted to NIH in connection with research grant proposals. We feel NIH should acknowledge receipt and disposition of the same so that the investigator and biohazard committee will have some firm basis for proceeding.

Sincerely,

Barbara E Echols

Barbara E. Echols
Secretary
Duke University Biohazards
Committee

cc: Dr. D. S. Fredrickson

SIERRA CLUB
330 PENNSYLVANIA AVE., S. E.
WASHINGTON, D. C. 20003

SIERRA CLUB

Washington, D.C. 20003
(202) 547-1144

October 26, 1977

Dr. Donald Fredrickson
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The meetings of the recombinant DNA advisory committee on December 15 and 16 are important enough to merit extensive public participation. For this reason, I would hope that the meetings could take the form of public hearings, with adequate provisions made for verbal contributions from interested participants. This format will work to further a thorough analysis of the proposed revised guidelines and their implications.

I hope you will consider this suggestion.

Sincerely,
Nancy E. Pfund

Nancy E. Pfund
Sierra Club Lobbyist
on recombinant DNA

R HARTZMAN
251 WEST 87 ST APT 52
NEW YORK NY 10024

western union Mailgram®

2-075560E300 10/27/77 ICS IPMMT77 CSP WSHC
2128659255 MGM TDMT NEW YORK NY 100 10-27 1048P EST

DR DONALD FREDERICKSON DIRECTOR
NATIONAL INSTITUTE OF HEALTH 9000 ROCKVILLE
PIKE
BETHESDA MD 20014

FRIENDS OF THE EARTH REQUEST THAT YOU WITHHOLD FURTHER ACTION ON THE PROPOSED REVISIONS TO THE RECOMBINANT DNA RESEARCH GUIDELINE- INCLUDING POSTPONEMENT OF THE DECEMBER 15-16 ADVISORY COMMITTEE MEETING- UNTIL AN ADEQUATE ENVIRONMENTAL IMPACT STATEMENT IS PREPARED, AND THAT, SUBSEQUENTLY, FORMAL PUBLIC HEARING BE HELD. TELEPHONE NUMBER 2128659255

RICHARD HARTZMAN
251 WEST 87 ST APT 52
NEW YORK NY 10024 TEL 2128659255

23:13 EST

MGMCOMP MGM

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : Dr. William Gartland

DATE: November 1, 1977

FROM : Maxine Singer

SUBJECT: Comments on the Draft Version of the Revised NIH Guidelines for Recombinant DNA Research, 6/23/77

Section I Introduction

Page I-1: First paragraph, last sentence. While I understand the purpose of the sentence to indicate one set of cases that are not novel, there is a little ambiguity. Thus, it will not usually be true that the "genomes" are known to replicate within an organism, rather, that sections or parts of the genomes may do so. A strict constructionist might have unnecessary trouble with this.

Footnote 1: Since the Introduction makes it clear that nothing is "not novel" until it is listed, it seems to me that the primary effect of this footnote is to remove flexibility even given the words "in general" at the start. I would suggest omitting the footnote.

Section II Containment

Page II-5, (7)...there appears to be a typo.

Page II-32, a. second sentence: "Natural environment" could be ambiguous, in practice. Presumable many of the host cells that people may wish to use have no natural environment other than the laboratory.

Section III Experimental Guidelines

Page III-2, item ii: Would footnote 4 be appropriate here? Note that there is an apparent paradox between this prohibition and the specific containment recommendations for experiments possibly involving chance production of recombinants containing genes for "potent toxin". I understand that the word "deliberate" is meant to make the necessary distinction, but wonder if it might be a little clearer.

Page III-4, a.(1)(a): Does this include tissue culture cells as a source of DNA, and if so, does it include transformed cells containing viral genomes? Is the situation different if the viral genome just happens to be there but is not the object of the cloning? And how about guidance for cloning the viral genomes themselves from such sources. Do these recommendations hold or those for viruses (page III-9) or ones similar to

those for retroviruses on page III-7. Note that page III-7 does answer the question for retroviruses but not for DNA viruses.

Also, what does free from infection mean? Free from all testable bacterial and viral infections? Or something more limited? Biohazards committees will need more guidance on this.

Page III-8, first full sentence. Some of these submissions may well be rather trivial. Perhaps then somewhat more flexibility should be put into the procedures for guidance to avoid unnecessary work by both the Office, the Committee, and the Director.

Page III-13, c.(1): The wording specifically omits purification by prior cloning, yet currently this is one of the best and most effective ways to purify.

Page III-16, 3a: Sentence beginning "Also, a recombinant...." is unclear as to intent.

Page III-21, (2)(b)(ii)...of the three conditions in (ii) the final one "previously cloned etc" omits certain ways of purifying the segment that are really just as satisfactory as cloning in a prokaryotic system or under P4. One of these is chemical synthesis, such as the somatostatin situation (note that the wording here seems inconsistent with (b) on page III-18, line 17). Another method is cloning by nature in natural recombinants between SV40 or Adeno and host DNA. A fourth would be highly purified repetitive eukaryote DNA which can be purified by restriction digestion and electrophoretic separation.

Section IV Roles and Responsibilities

Page IV-6 and -7. The reasons for adding the requirement for an institutional biological safety officer are not made clear either in the Guidelines or in the Draft "Comparison" document. Without some compelling reasons, which do not occur to me, I believe that this added complexity is not warranted. While large institutions may wish to have such an individual to support the work of the Biohazards Committees, it will be quite a burden in smaller institutions. Further, it seems to me that each Institution, large and small, is in a better position than the NIH to develop operating procedures for itself. For example, different members of the Institutional Biohazards Committees might be appointed responsibility for the various individual tasks given the Safety Officer here. Inevitably, there will be added levels of review and paper work with the suggested system not to mention the unfortunate idea of a "policeman". I recommend omitting this requirement, or at the most, making it an optional suggestion.

Page IV-9, E. (c): Memorandum of Understanding and Agreement is not defined. This is the first and only time the expression is used in the revised Guidelines.

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOCHEMISTRY
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Area Code 415
497-6161

November 2, 1977

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The following are my comments on the new proposed NIH guidelines for recombinant DNA research.

1) Use of HV designation. I am happy to see this essential change.

2) DNA containment, page 49603(5). This section is a disaster, and if it remains in the guidelines, it could undermine their credibility. DNA is not an organism, it is a chemical. Handling a chemical by "good microbiological technique" is absolutely ridiculous.

a) It is assumed in these guidelines that the reason recombinant DNA may be potentially hazardous is that such recombinants cannot be generated by "natural" means. From present experimental evidence we know that if DNA can enter cells, recombinant DNAs are readily generated. Therefore, if DNA can naturally enter cells, then recombinant DNA cannot be hazardous. If DNA cannot naturally enter cells, then again the DNA cannot be hazardous.

b) Dead organisms contain DNA. I find it absurd to think that a live organism containing recombinant DNA that is handled at the P1 and P2 levels must also be handled at the P1 level after it is dead.

c) One of the major containment techniques is to kill the organisms early in the course of an experiment and to then extract their DNA. Under the new guidelines, this containment technique would have to be abandoned as ineffective. I think this is wrong.

d) Autoclaving DNA poses grave health hazards to research personnel (probably far greater than any live organism containing recombinant DNA). For example, most DNA samples that are to be disposed of contain ethidium bromide and ^{32}P. Contamination of autoclaves with these materials could be quite dangerous.

3) Physical containment. The containment protocols have been escalated. The new P1 is almost identical to the present P2. I strongly feel that the changes in the requirements for physical containment is a serious matter and should not be done unless clear justification is given. Such justification is not given. Why are the physical containment levels being raised? Will all experiments soon require present P3 level containment?

I hope my comments are of help to you; I feel that they are very important and request that you treat them seriously.

Sincerely yours,

Ronald W. Davis
Associate Professor of Biochemistry
(I was one of the original eleven signers of the Science Biohazard Letter.)

RWD/lh

STATE OF CALIFORNIA—HEALTH AND WELFARE AGENCY EDMUND G. BROWN JR., Governor

DEPARTMENT OF HEALTH
714-744 P STREET
SACRAMENTO, CALIFORNIA 95814
(916) 445-8706

November 7, 1977

Honorable Adlai Stevenson
United States Senate
Washington, DC 20515

Dear Senator Stevenson:

Thank you very much for the opportunity to appear before the Commerce Committee which you chair. I felt that the quality and seriousness of our deliberations was much enhanced by your patience and astute questioning.

I would like to expand on one of my remarks which I did not have an opportunity to explore fully because of time constraints. As one of my recommendations, I urged the Committee to consider introducing legislation by which Congress would declare recombinant DNA organisms to be a national resource. The purpose of such a declaration would be to ensure that the study, development and, ultimately, mass scale production of recombinant organisms would take place orderly and systematically, in a climate of maximum safety, openness and cooperation. Licensure and dispensation of all newly constructed organisms could be accomplished in much the same way as the Atomic Energy Commission (AEC) handles radioactive isotopes and primary nuclear fuels. Indeed, the rationale for establishing the AEC, namely to protect the public welfare and to ensure the safe development and deployment of potentially beneficial yet hazardous materials, could reasonably be extended to recombinant DNA organisms.

Perhaps more pertinently, each cloned recombinant organism will almost always be a unique bacterial strain or even a new species of life, with the capacity to generate its own kind, but rarely (if ever under present technologies) to be duplicated by reconstruction through fresh syntheses. This last character is virtually guaranteed for organisms produced by "shot-gun" approaches, where the entire genome of an organism is enzymatically fragmented, to be scavenged or inserted at random into a vector or bacterial host. The interest of the drug companies in patenting novel organisms produced in such a way bespeaks the importance and uniqueness of their construction. The protection of such newly made recombinant organisms might be seen in the light of the protection afforded rare species under the Endangered Species Act.

A repository for recombinant DNA organisms, much like those established for human cell lines, is in fact being established under the auspices of NIH under the direction of Dr. Fred Bergmann. Making every organism with unique genetic properties available for study would be a tremendous boon to science -- and to industrial interests. Both could obtain them, subject to reasonable constraints under license, from a Federal commission. Such a commission could thereby insure that the conditions of use and responsible personnel were consonant with appropriate principles and guidelines (e.g., the NIH Guidelines for Conduct of Recombinant DNA Research).

Pursuant to an Act of Congress, a broadly constituted Recombinant DNA Commission could be given the following charges:

1. promulgate and review uniform rules and regulations for the conduct of recombinant DNA research;

2. license and monitor all laboratories which conduct recombinant DNA work involving de novo production of organisms;

3. perform periodic reviews of the nature and necessity of safety precautions taken for various research modalities;

4. direct appropriate monitoring and safety personnel to review the health of workers in licensed laboratories;

5. establish and maintain appropriate regional centers or licensed laboratories to be repositories for banks of recombinant DNA organisms;

6. establish fees and appropriate licensure requirements for laboratories which wish to use pre-existing organisms; and

7. ensure ongoing and meaningful public access to the newly constructed organisms, records and deliberations of any commission established to deal with recombinant DNA research.

A more detailed charge and construction of any legislative proposal would of course be needed. But, were Congress to act to place recombinant DNA organisms under federal control, with due allowance--and encouragement--of scientific inquiry, many of the problems generated by too rapid exploitation of this invaluable resource could be avoided.

Like nuclear and geothermal energy, organisms created through recombinant DNA technology are an invaluable national resource, too precious to be usurped and patented by private corporations or to become the sole property of individuals. Each organism embodies novel knowledge, and as such "belongs" to the public.

I commend this concept of protecting recombinant DNA organisms to the attention of your Committee as one way of responsibly protecting public health while guaranteeing free and open access to organisms with unique and potentially desirable properties.

Sincerely,

Marc Lappe' Ph.D., Chief
Office of Health, Law and Values

cc: Donald Frederickson
Director, NIH
Bethesda, MD 20014

Clifford Grobstein, Ph.D., Professor
Biological Science and Public Policy
Department of Biology
University of California, S.D.
P. O. Box 109
La Jolla, CA 92037

ELI LILLY AND COMPANY

INDIANAPOLIS, INDIANA 46206

C. W. PETTINGA, Ph. D.
EXECUTIVE VICE PRESIDENT

November 7, 1977

Donald S. Frederickson, M. D.
Director
National Institutes of Health
Department of Health, Education, and Welfare
Bethesda, Maryland 20014

Dear Don:

Enclosed are our comments on the proposed revisions in the NIH Guidelines on Recombinant DNA Research. An identical copy has been furnished to the Pharmaceutical Manufacturers Association which will comment on behalf of a number of companies.

Since the moratorium on research involving recombinant DNA and the publication of the initial guidelines, several aspects of this situation have become increasingly obvious. Recombinant DNA research will not be as dangerous to mankind as initially postulated by its opponents. Also, the potential benefits to mankind may not be as rapidly achieved as originally thought by the proponents.

Although Lilly has supported the concept of legislation to provide for the licensure of recombinant DNA research facilities, certain of the legislative proposals currently before the Congress do cause our scientists concern. The regulation of research, i. e., the regulation of inquiries to establish new knowledge, is an extremely difficult task and must be approached with great caution to avoid inhibiting the growth of knowledge. We continue to believe that research is best left unregulated but, if licensure of some sort is necessary, that the restrictions on responsible laboratories be minimal.

We appreciate the opportunity to comment on the proposed revisions in guidelines. We are also grateful for the objective, intelligent leadership that you and other members of the National Institutes of

Health have demonstrated in handling problems associated with recombinant DNA research both from the scientific and public standpoint.

With best personal regards.

Very truly yours,

C. W. Pettinga

sas

Enclosure

Comments on the Proposed Revision

of the Guidelines for Recombinant DNA Research

We respectfully offer the following comments, both general and specific, on the proposed revision of the guidelines:

A. General.

The NIH Guidelines for Recombinant DNA Research as presently constituted do not apply to research in this area conducted in private industrial laboratories; nevertheless, the spirit and intent of the guidelines has been and will continue to be followed by these groups. If, at some time in the future, complete adherence to the guidelines becomes mandatory for all laboratories involved in recombinant DNA research certain procedures in the guidelines pose a difficult problem in terms of patentability of new concepts and protection of proprietary interests. With the few exceptions discussed in later specific comments, compliance with all other features of the guidelines appears reasonable.

We wish to emphasize, however, that we also have great concern for the lack of protection afforded information developed through academic, government-funded research. To be in the public interest, more is required of government-funded research than the investigation, development and refinement of recombinant DNA techniques for producing, say, insulin or pituitary hormone by these means. The public interest is served in part when the research from academic institutions is subjected to the investigation, development, and refinement

necessary for carrying out these processes on a commercial scale and for producing from them the products that ultimately define such contributions of recombinant DNA research to the public.

The early public disclosure that would result from the submission of research hypotheses, designs and protocols and of data as work progresses, without protection against its public dissemination, would frequently preclude later patent protection otherwise available to the university for licensing to a commercial organization that would carry the work forward. This, in turn, would limit the feasibility of commercial investment in research and production facilities. We therefore express a common concern with the academic community that lack of confidentiality would dissipate the rights that would later form the basis for bringing the fruits of this research into practical use for the benefit of the public.

As a general feature of the revision, then, we recommend the insertion of an acknowledgment that premature disclosure of hypotheses, protocols, designs, data, or other research results will have a discouraging effect on research incentives. In identifying such disclosures, we differentiate between those findings which provide for greater safety and consistency in the conduct of recombinant DNA research--and those which embody the potential for commercial use through production of a desirable product. It is important not to unduly restrict the former while protecting the latter.

B. Specific Comments.

The paragraph notations in the following part of these comments correspond to that appearing in the "Recombinant DNA Research Proposed Revised Guidelines", Federal Register, September 27, 1977, part III.

I. Introduction.

We are in agreement with the exclusion of recombinant DNA molecules formed from any combination where the components are derived from genomes known to replicate within the organism used to propagate the recombinant molecules; however, we would suggest adding to the non-excluded exceptions described in footnote 1. those DNA's derived from recombination experiments involving bacterial pathogens.

* * * * * * *

The question of protection of confidential information as it affects commercial, competitive enterprise arises throughout the guidelines and the proposed revision. We recommend that an acknowledgment of the need for such protection be recognized and that suitable statements be included in the introduction to ensure confidentiality when necessary. Under the Freedom of Information Act, research protocols, designs, data, and other research results become publicly available within the context of the current and proposed guidelines. If the guidelines are extended to cover non-federally funded research, provision must be made to protect proprietary interests.

Sections of the guidelines where such statements would apply include but are not limited to:

II., D., 3. - Distribution of Certified Host-Vectors.

III., B., 1., c. - Lowering of Containment Levels...

IV., A., 1st paragraph, subsection (vi) Submitting Information...

IV., B., 5th paragraph - Minutes of the Meetings...

II. Containment.

D. Biological Containment.

1. Levels of Containment.

a. HV1.

In general, this section is rather vague. What specifically is meant by "low potential for survival?" Also, are HV1 hosts meant to be wild type organisms or are they meant to harbor containment mutations? If HV1 host-vector systems are meant to be wild type, we propose that this section might, for example, be reworded as follows: "Hosts should be wild type species or derivatives thereof which are non-pathogenic for plants or animals and which do not contain conjugative plasmids or generalized transducing phage. Vectors should be non-conjugative plasmids or bacteriophages". If HV1 hosts are intended to harbor containment mutations, then we propose that an HV0 host-vector system be defined. An HV0 system could then employ a wild type non-pathogenic organism with a non-conjugative plasmid or bacteriophage vector. Experiments requiring P2+HV1 could then be carried on under P3+HV0 containment. We also suggest that HV0 systems should not require certification by the NIH, but approval at the local biohazards committee level.

3. Distribution of Certified Host-Vectors.

This section should also include new certified HV1 host-vector systems.

III. Experimental Guidelines.

B. Containment Guidelines for Permissible Experiments.

1. Classification of Experiments using the E. coli K-12 Host-Vector System.

a. Shotgun Experiments.

2. Prokaryotic DNA Recombinants.

This section remains unnecessarily restrictive and is inconsistent with the section on lower eukaryotic DNA's. We suggest eliminating the requirement for "extensive characterization" which could inadvertently eliminate all prokaryotic DNA's other than those of E. coli, λ, and T4 from the minimum containment of P2+HV1. Surely "shotgun" experiments to clone DNA from one non-pathogenic bacterium to another cannot pose a greater potential risk than "shotgun" cloning of plant or fungal DNA into a bacterium. We propose that cloning of DNA from non-pathogenic prokaryotes requires only P2+HV1 or P1+HV2 containment. Cloning of DNA from Class 2 organisms could retain the P3+HV2 containment requirement. However, care must be taken not to inadvertently include harmless micro-organisms as Class 2 agents (see comments below on classification of Actinomycetes), since misclassification would impose the unfortunate and unnecessary requirement of increasing both the

physical and biological containment by one step. In practice, this could effectively block any recombinant DNA research with the therapeutically and economically important Streptomyces, since HV2 host-vector systems of this type will most certainly not be available for some time. Under these circumstances, the first paragraph of section III., B., a., 2. would not then be needed.

c. Lowering of Containment Levels for Characterized or Purified DNA Preparations and Clones.

1. Purified DNA Other than Plasmids, Bacteriophages, and Other Viruses.

The first sentence of the last paragraph of this section could be modified in some manner to read, for example: "The institutional biohazards committee (IBC) must review and may approve such a reduction".

IV. Roles and Responsibilities.

D. NIH Recombinant DNA Molecule Program Advisory Committee.

The last sentence of the third paragraph of this section could be modified to take into account expertise in the field, for example: "In making recommendations for exceptions, weight will be given to scientific and societal benefits, potential risks, and to industrial experience with large scale production of pathogenic organisms and toxic materials". This same modified statement should also appear in Section III., A., third paragraph.

Appendix B.

2. Fungal Agents.

Actinomycetes are bacteria, not fungi, and include numerous genera and an extraordinary number of species, the vast majority of which are non-pathogenic (for reference, consult any standard microbiology text and ref. 1). For instance Bergies Manual of Determinative Bacteriology (1) describes 416 species and 47 subspecies of Streptomyces, while only four species are considered human pathogens (2). To avoid inadvertent classification of harmless Streptomyces and other harmless Actinomycetes of therapeutic and economic importance as Class 2 Agents, we suggest that only the pathogenic Actinomycetes be listed as Class 2 Bacterial Agents. Below is a summary of pathogenic Actinomycetes listed in ref. 2, 3, and 4:

Actinomyces eriksonii

Actinomyces israelii

Actinomyces bovis (bovine pathogen)

Actinomyces naeslundii

Actinomyces odontolyticus

Actinomyces suis (swine pathogen)

Actinomyces viscosus

Arachnia propionica

Dermatophilus congolensis

Nocardia asteroides

Nocardia brasiliensis

Nocardia caviae

Streptomyces niadurae

Streptomyces pelletierii

Streptomyces paraguayensis

Streptomyces somaliensis

References

1. Bergies Manual of Determinative Bacteriology, 8th Edition. Eds. R. E. Buchanan and N. E. Gibbons. Williams and Wilkens: Baltimore. 1974.

2. Bacterial and Mycotic Infections of Man, 4th Edition. Eds. R. J. Dubos and J. G Hirsch. Lippincott: Philadelphia. 1965.

3. Fundamentals of Medical Bacteriology and Mycology. Eds. Q. N. Myrvik, N. N. Pearsall and R. S. Weiser. Lea and Febiger: Philadelphia. 1974.

4. Actinomyces, Filamentous Bacteria. Biology and Pathogenicity. Eds. J. M. Slack and M. A. Gerencser. Burgess: Minneapolis. 1975.

AREA CODE 608
PHONE 262-2177

McARDLE LABORATORY
FOR CANCER RESEARCH

MEDICAL CENTER UNIVERSITY OF WISCONSIN · MADISON, WISCONSIN 53706

November 8, 1977

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

As a former member of the Advisory Committee, who is not performing novel recombinant DNA research, I would like to make a few comments and suggestions pertaining to the Proposed Revised Guidelines as published in the Federal Register 42 No. 187 of September 27, 1977, pp. 49596-49609.

The area covered by the Guidelines can be divided into research employing (A) E. coli K-12 host-vector systems and (B) other host-vector systems. Based on the data presented in the "Curtiss letter" and the conclusions of the Falmouth Meeting there is no real justification to include most novel recombinant DNA activities employing systems (A), i.e., E. coli K-12 EK1 or EK2 host-vector systems, into the Guidelines. This is what we meant by stating in the Introduction that "the revised Guidelines continue to be deliberately restrictive, with the intent of erring on the side of caution". However, I have grave doubts whether scientists or the U. S. Government, represented by the N.I.H., have a right to "intentionally err" just to accommodate irrational fears, concerns and politically motivated considerations.

There are two solutions to this dilemma. One would be just to modify or eliminate the words "with the intent of erring" without changing the Guidelines. This would be a very wrong solution even if the present Committee could be persuaded to change the wording. It was a unanimous decision after long deliberation and new members would not be aware of all the reasons for this statement. The second solution would be to change the statement "with the intent of erring", but at the same time to exclude from the Guidelines all novel recombinant DNA activities employing E. coli K-12 EK1 or EK2 host-vector systems, with the exception of (1) those DNAs listed in IIIA, (2) DNAs derived from true pathogenic strains of class 2 (Appendix B), and (3) DNA from organisms known to produce hazardous polypeptides (toxins or other agents of pronounced biological activity and known to be highly active when ingested).

I strongly urge you to adopt this second solution, since there is no reason to hamper very beneficial research employing many important organisms for which no practical hazards could be logically conceived, just because of a few isolated cases where some scary scenarios could be imagined. Let's include these few isolated cases (as specificed above under (1) to (3)) under the Guidelines and exclude from the Guidelines all other E. coli K-12 EK1 and EK2 host-vector-based experiments.

One requirement could be instituted for these latter experiments: to register them with the N.I.H. and local Safety Committees on one-page forms specifying (1) name and address of all investigators, (2) cloned DNA, (3) host-vector system (4) physical containment, (5) purpose of the experiments, and (6) dates covered by the registration. Such registration would have to be filed concurrently with the initiation of the experiments, but no specific approvals would be required.

The reasons I urge you to institute this change in the proposed Guidelines are at least twofold:

(1) There is no logical justification to control the great majority of safe and beneficial experiments on the basis of "guilt by association" with a few questionable experiments arbitrarily placed in the same class (see Hogness' letter and the P.S.). It is better to treat the questionable experiments separately, by including them in the Guidelines.

(2) The Guidelines seriously interfere with many experiments, and a few latest examples of that are represented by letters of Dr. R. Palmiter (study of purified chicken ovalbumin gene), S. Cohen (study of dihydrofolate reductase) and B. W. O'Malley (characterized clones of ovalbumin DNA) reviewed at the November 1, 1977 meeting of the Advisory Committee. No dangers could even be imagined for the proposed experiments, but nevertheless they will be seriously delayed or blocked. Moreover, there is a useless expenditure of taxpayer's money and the loss of time by the investigators, N.I.H., and the Committee on preparing applications, processing and considering them, where there is no logical need for all these bureaucratic evaluation procedures.

I sincerely hope that the present golden opportunity will not be lost to exclude from the regulations all the novel recombinant DNA experiments where no practical dangers could be even imagined (cloning of Saccharomyces yeast DNA, Drosophila fly DNA, DNA of laboratory animals like mice or rats, specific human DNA), whereas the scientific and social benefits are great. Otherwise, history will cast us in the position of Colonel Nicholson defending "The Bridge on the River Kwai" or of courtiers in the Hans Christian Andersen story about "The Emperor's New Clothes".

With the warmest personal regards,

Sincerely yours,

Waclaw Szybalski
Professor of Oncology

WS:mb

P.S.: I read the letters of Drs. Paul Berg (June 14, 1977), Maxine Singer (June 21, 1977) and David Hogness (June 23 and 30, 1977), which were included in the material for the Advisory Committee for the November 1, 1977 meeting. I agree with most aspects of these letters and especially endorse those parts of Dr. Hogness' letter which (a) warn us that categorizing experiments in the Guidelines was arbitrary, misplacing some experiments, (b) the original Guidelines, as drafted, were a "conservative guide to common-sense precautions against speculative hazards, where considerable leeway is expected and allowed", and (c) it is unfortunate that these Guidelines were "converted into legal regulations", "in the emotional and often hysterical atmosphere engendered by opponents of this research". At present there are only a very small number of such opponents, mostly very vocal and politically motivated, whereas the overwhelming majority of informed scientists are against legal regulations, as shown by the resolutions prepared by participants of several Gordon Conferences and by the National Academy of Sciences.

I also endorse Dr. Hogness' suggestion that experiments assigned to the P1 and P2 containment should not require "M.U.A's and all of the attendant bureaucratic paraphenalia"; a one-page registration as described earlier in this letter would be the maximum requirement.

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Medicine

November 9, 1977

Donald S. Fredrickson, M.D.,
Director,
National Institute of Health
Building 1, Room 124
BETHESDA, Md. 20014

Dear Don:

I believe the proposed revisions of the NIH Guidelines on recombinant DNA research, as recently published in the Federal Register, represents a substantial improvement over the earlier version of the Guidelines. However, I do have a few comments and suggestions about the revisions.

(1) Definition of Recombinant DNA. There is an ambiguity in the proposed definition of "novel recombinant DNA." In order for a recombinant DNA molecule not to be considered novel, the Guidelines require that all of its components be derived from species that are known to exchange chromosomal DNA by natural physiological processes. This suggests that even if plasmids can be exchanged between two bacterial species by physiological processes, recombination of plasmid DNA segments in vitro is considered "novel" if exchange of chromosomal DNA has not also been demonstrated. However, further down in the same paragraph there is the statement that "all recombinant DNA molecules formed from any combination of DNAs will not be considered novel when all components are derived from genomes known to replicate within the organism used to propagate the recombinant DNA." This sentence implies that plasmid recombinants would not be considered novel if the plasmids can be exchanged, regardless of whether exchange of chromosomal DNA can occur. I think this apparent contradiction needs to be resolved.

My suggestion would be to define "novel recombinant DNAs" as follows: "molecules that consist of segments of any DNA from different species that are not known to exchange DNA by natural physiological processes." I know of no scientific basis for suggesting that organisms known to exchange extrachromosomal genetic information cannot also transfer chromosomal genes. Transduction and intracellular recombination between chromosomal and extrachromosomal DNA are well recognized biological processes.

The modification I suggest would remove any ambiguity and would eliminate the apparent contradiction with the statement contained later in the paragraph 1 of the "Introduction" section of the Guidelines.

(2) Other host vector systems. Many of the practical benefits of recombinant DNA will depend on the ability to manipulate genes within organisms that produce medically and biologically important products such as antibiotics. The development of cloning systems in such species is, in my opinion, of great value. Yet, in revising the guidelines, the authors of the section on "Other host vector systems" seem to have given little consideration to the importance of being able to manipulate the genes of such species per se, and have instead dealt with other host vector systems simply as possible alternatives to E. coli for the cloning of genes of higher organisms.

The revised guidelines state that cloning in host vector systems other than E. coli must use strains that have "low potential for survival in their natural environment," regardless of the lack of pathogenicity of the species or the nature of the natural environment of that species. This appears to be a direct transfer with little additional thought of considerations pertaining to the use of E. coli K12 for recombinant DNA experiments. I think it is important to recall that the "low survival" attributes of E. coli K12 were initially put forth as a response to those who had concerns about using a bacterial strain that they believed might inhabit the human intestine. At that time, critics proposed that only bacterial species unassociated ecologically with humans or with domestic animals should be used. Subsequently, data has been presented to indicate that E. coli K12 has little, if any ability to colonize the human gastrointestinal tract. Somehow, in the course of events, the argument that it is safe to use E. coli K12 as a host because it does not colonize the human intestine, has been distorted. The statement is now being made that E. coli K12 should be the only approved host, and that other bacterial species -- no matter how non-pathogenic and remote from human ecology -- must not be used unless it is specifically demonstrated that the recipients have a low potential for survival in their natural environment (whatever that environment may be).

I believe that this new requirement will seriously impede and perhaps entirely cripple work aimed at using a variety of non-pathogenic bacteria as hosts in experiments aimed at improving the quality or quantity of biological products made by those bacteria. For example, an experiment involving the introduction of genes by recombinant DNA methods from Streptomyces coelicolor to Streptomyces lividans, in order to design a more effective antibiotic, could simply not be done in the wild type antibiotic-producing strain at any level of containment whatsoever.

These two organisms, although both closely related members of the genus Streptomyces, have not been shown to exchange DNA by natural physiological processes, (although DNA can be exchanged by experimentally induced cell fusion) and gene exchange by in vitro methods would come under the NIH Guidelines. Since the wild type recipient strain Streptomyces lividans does not have "low potential for survival in its natural environment", it could not even be classified as an HV1 system. Thus, even though there would probably be unanimous agreement by scientists that the experiment I've described above poses virtually no risk whatsoever, the experiment could not be carried out, even under high levels of physical containment, under the proposed Guidelines. By defining an HV 1 system in an inappropriate way, the authors of the revised Guidelines effectively have included recombinant DNA experiments with wild type non-E.coli hosts in the list of "prohibited experiments". Certainly the advisory committee could not have intended to place a Streptomyces coelicolor-Streptomyces lividans recombinant DNA molecule on the "too dangerous to be done" list, while at the same time permitting the cloning of DNA from a wide variety of animal cell and viral sources in E. coli K12 under minimal to moderate containment conditions. Yet, this is precisely the inevitable effect of the wording currently used. I urgently ask that you resolve this serious inconsistency prior to approval of the revised Guidelines.

I suggest that the problem can be resolved by simply having the Guidelines state that "wild type isolets of any bacterial species not known to be pathogenic to humans, to domestic animals, or to agriculturally important plants may be used as an HV1 host-vector system, provided that all components of recombinant DNA molecules introduced into such a host vector system, are derived from other prokaryotic organisms within Etiologic Agent Class 1. Use of a non-E.coli HV system for the propagation of genes derived from organisms other than those included in Etiologic Agent Class 1, or which are derived from eukaryotic organisms, shall be subject to certification as described in the Guidelines."

I believe this modification will provide adequate safety while still enabling work of great importance and minimal hazard to proceed.

(3) Levels of biological and physical containment for certain experiments. In most instances, the investigator is given the option of using either P2 + EK2 containment or P3 + EK1. However, in the section dealing with shotgun experiments from mammals other than primates (page 49601 of the Federal Register, September 27, 1977), and in the experiments dealing with DNA from birds, there is no option of trading a higher level of physical containment for a lower level of biological containment. Depending on the gene to be cloned, there may be legitimate and compelling experimental reasons for an investigator to wish to use P3 + EK1 for such experiments, rather than P2 + EK2. For example, the approved EK2 host (or hosts) may not be suitable for detection of the gene to be cloned (e.g. the thy A mutation of X1776 prevents detection of expression of mammalian genes coding for the enzyme dihydrofolate reductase, since the host bacterial strain is already resistant to trimethoprim and methotrexate).

I believe that, for consistency, the Guidelines should give investigators the option to trade a level of physical containment for a level of biological containment in these categories, as they have done in others. If the principle of making such a trade is valid, it should be applied across the board.

(4) The institutional committee to be established in connection with recombinant DNA should be called an institutional biosafety committee, rather than a "biohazards" committee. It seems to me that the purpose of the institutional committee is to ensure the biosafety of recombinant DNA experimentation, whether or not biohazards are actually involved. Since the introductory section clearly points out that "to date, no known hazardous organism has been produced in this work," the term "biosafety committee" would seem to be more appropriate and would more accurately describe the responsibility of the committee. Continued use of the term "biohazards committee" helps to foster fears which, in my opinion, do not appear to be warranted.

I hope that these comments and suggestions will be useful to you and to the Advisory Committee in preparing the final version of the revised Recombinant DNA Guidelines.

Sincerely yours,

Stanley N. Cohen, M.D.
Professor of Medicine and
Professor of Genetics

SNC/jmd

CSU

Department of Botany and Plant Pathology
303/491-6524

Colorado State University
Fort Collins, Colorado
80523

November 10, 1977

Dr. Donald S. Fredrickson, Director
Department of Health, Education, and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This is in response to your memo of October 26, 1977 requesting review of proposed revisions of the NIH Guidelines.

Section III A designates experiments that are not to be performed. One of these is "Deliberate creation by the use of recombinant DNA of a plant pathogen with increased virulence and host range beyond that which occurs by natural genetic enchange" (probably exchange).

Virulence is usually defined as extent in time and severity of pathogenicity. It's a degree or measure of pathogenicity. In this context, pathogenicity is assumed even though virulence may be very low. Thus the wording in the guidelines appears to allow one to take an organism that is not a pathogen and convert it to a pathogen. This might be stretching a point but I gather the NIH Guidelines is at least a semilegal document (and may be adopted in legislation) and should contain wording that is not susceptible to misinterpretation.

I hasten to add that the wording in the guidelines may be carefully designed to allow research on conversion of nonpathogens to pathogens. Benefits from such research may outweigh hazards. One could conjure up all kinds of exciting experiments using recombinant DNA to test the common antigen hypothesis, for example.

It would seem that section III, A, iii has been violated already. Plasmids from a virulent isolate of the crown gall bacterium were transferred to an avirulent strain rendering the latter virulent. This is increasing the virulence of a plant pathogen (as a separate entity) and not a species, however, and I see no reason to ban research of this nature. Perhaps it would be more lucid to use the phrase "species of plant pathogen" rather than "plant pathogen" alone.

Sincerely,

Ralph Baker

Ralph Baker
Professor of Botany and Plant Pathology

RB/cvh
CC: Martin Alexander
Peter R. Day
Joel Fisher

THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF HYGIENE AND PUBLIC HEALTH
615 North Wolfe Street
Baltimore, Maryland 21205, U.S.A.

DEPARTMENT OF BIOCHEMISTRY
(301) 955-3671

November 10, 1977

Dr. Donald S. Fredrickson
Director, National Institute of Health
Bethesda, Maryland 20014

Re: Revised Recombinant DNA Guidelines

Dear Dr. Fredrickson:

Those of us on the Institutional Biohazards Committee have found it difficult to identify all the changes proposed in the Guidelines issued September 27, 1977. It would be helpful if in the final form the changes were boldly identified. If not that, a list of the changes accompany each copy.

I apologize for the tardiness of this comment.

Sincerely yours,

Roger M. Herriott

Roger M. Herriott
Chairman, J.H.U.
Biohazards Committee

RMH:mam

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director, NIH

DATE: November 11, 1977

FROM : Wallace P. Rowe, M.D.

SUBJECT : Comments on Proposed Revised Guidelines for Recombinant DNA Research as published in Federal Register September 27, 1977.

As you know, I am a member of the Committee that prepared the revised guidelines. On rereading them I noted some generally minor points that need clarification, and I am writing as an individual to bring them to your attention.

The recommended changes, and the reasons therefore are as follows:

1. p. 49601, Col. 3, line 24. Change the phrase in parentheses to read: "(i.e., not productively infected as demonstrated by standard assays for the common viruses of the species under study)".

- This clarifies what the investigator must do to meet the requirement.

2. p. 49602, Col. 2, line 84. This section should cross reference to the stated requirements for lowering containment for clones with DNA inserts from viruses of eukaryotes, in order to make it clear that the proposed mechanisms apply to these containment reductions and are not in addition to them. This could perhaps be handled by adding this sentence at the end of col. 3, line 2: "Criteria for lowering containment conditions for clones containing DNA from viruses of eukaryotes were given in section III.B.1.b.(1)."

3. p. 49602, Col. 3, line 58. Change the word "infectious" to "progeny".

4. p. 49602, Col. 3, line 61. Change the word "significant" to "a high degree of".

- This eliminates confusion as to why SV40, Ad.2, and Ad.5 are not disqualified; they can be pathogenic, but are not highly pathogenic in any sense of the term.

5. p. 49602, Col. 3. In the sentence beginning on line 78, the antecedent of "limitation" is not immediately clear. It would help to change the sentence to read: "Subject to the limitation in (i) above, (that is, that the genome not be from an agent that is infectious for humans or that replicates to a significant extent in human cells in tissue culture), it is not required...

6. p. 49603, Col. 1, line 69. Insert after "above)":
" , except that it is not required that the virus be unable to replicate in mouse cells".

- This removes an unnecessary restriction which is valid for polyoma virus but not for viruses that will not be studied in mouse cells and which will be worked with in P4.

7. p. 49603, Col. 2. After line 27 insert:

"(3) Mouse adenovirus as a candidate vector. This virus may qualify in the near future as a cloning vector, and would offer distinct safety features. In particular, the fact that insofar as is known, it replicates only in mouse cells makes it a desirable vector. If additional data are obtained which in the judgment of this Committee show that mouse adenovirus meets the general requirements above, it can be used as a cloning vector under the conditions specified for polyoma virus in section III.B.3.(1) above."

- This is a possibly important new development and should not be excluded from the guidelines.

8. p. 49603, Col. 2, line 57. After the word "if" insert: "in the judgment of this Committee"

- This clarifies the mechanism for making the decision as to whether the data are adequate.

A copy of the Register with the locations marked is attached.

I am sending a copy of this to the Committee members for their possible comments.

Wallace P. Rowe, M.D.

1 Encl
as

sg

November 14, 1977

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have been following with special interest the development of proposed NIH Guidelines for Recombinant DNA Research. This letter is in response to your public invitation for comments on your proposed revisions to such Guidelines, as published in the Federal Register of September 27, 1977.

My comments pertain to revised Section IV, Roles and Responsibilities.

While I was very pleased to have noted in that Section the "addition" of a requirement for a BIOLOGICAL SAFETY OFFICER, I am disappointed that the NIH Guidelines do not propose also the additional requirement for a BIOHAZARDS CONTROL SAFETY MANAGER. The need for two such distinct positions and responsibilities has long been recognized by CDC. Moreover, at CDC such incumbents are also separated by unlike duties as EX-OFFICIO MEMBERS OF THE BIOHAZARDS COMMITTEE.

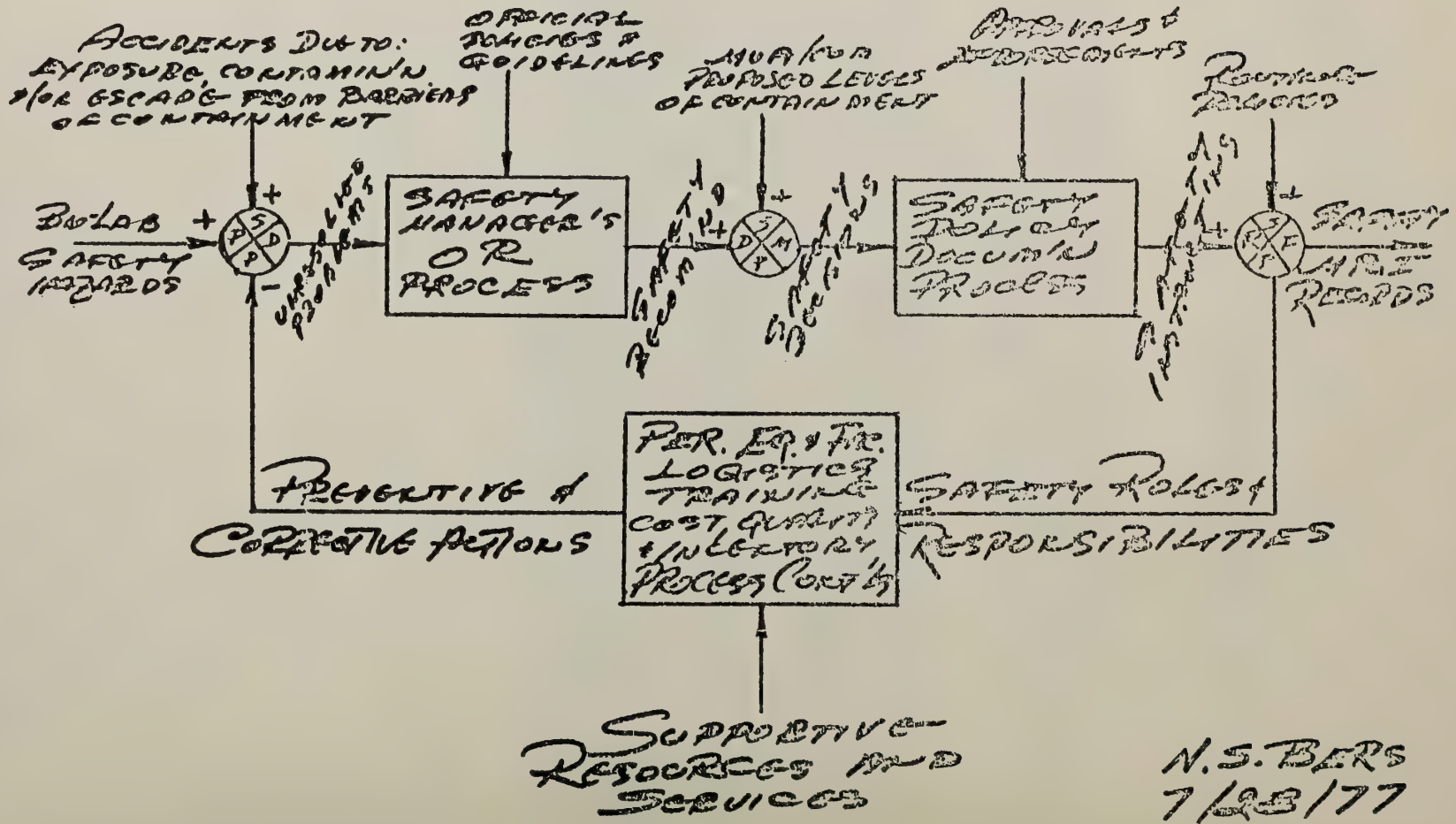
I believe that the NIH Guidelines should include an additional requirement for the position of a BIOHAZARDS CONTROL SAFETY MANAGER, as CDC does, and that an NIH exemplary initiative to such effect may be most appropriate for demonstration in the Gudelines ... and through its own actions. As illustrated in my attached information-flow-block-diagram, proposed for inclusion in the NIH Guidelines of the next revision, a SAFETY MANAGER's primary concern would be to maintain a systematic approach to continuing improvements in the development, implementation, and management of programs aimed to evaluate for preventive and corrective actions the safety of any ongoing high containment Recombinant DNA Research procedure, at revised MUA levels of corresponding biological and physical levels of containment.

Sincerely yours,

Naum S. Bers, Ph.D.
P.O. Box 1692
Rockville, Maryland 20850

•Attachment

PROPOSED BIOHAZARDS MANAGEMENT CONTROL SYSTEM, BLOCK-DIAGRAM.


ACCIDENTS DUE TO: EXPOSURE, CONTAMINATION &/OR ESCAPE FROM BARRIERS OF CONTAINMENT
OFFICIAL POLICIES & GUIDELINES
MAXIMUM PROPOSED LEVELS OF CONTAINMENT
APPROVALS & DISAPPROVALS
FEEDBACK RECORD
BIOLAB SAFETY HAZARDS
SAFETY MANAGER'S OR PROCESS
SAFETY ROLE OF DECISION PROCESS
SAFETY RECORDS
PER. EQ. & FAC. LOGISTICS TRAINING COST, QUALITY & INCENTIVE PROCESS COSTS
PREVENTIVE & CORRECTIVE ACTIONS
SAFETY ROLE & RESPONSIBILITIES
SUPPORTIVE RESOURCES AND SERVICES
N.S. BERS 7/28/77

NATIONAL SCIENCE FOUNDATION
WASHINGTON, D.C. 20550

November 14, 1977

Dear Don:

We distributed approximately 200 copies of the draft revised guidelines to our staff, consultants and selected grantees for comment. Enclosed are the responses. I can't imagine your response ratio was similar.

Sincerely yours,

Herman W. Lewis
Senior Scientist for
Recombinant DNA

Enclosure

UNITED STATES GOVERNMENT

memorandum

DATE: November 14, 1977

REPLY TO ATTN OF: Developmental Biology Panel

SUBJECT: Comment on draft revision of the NIH Guidelines

TO: Herman W. Lewis
Senior Scientist for Recombinant DNA

When considering plant systems as possible recipients of recombinant DNA molecules, the guidelines should distinguish between plant cells and protoplasts. The latter are a giant step in the direction of biological containment since they cannot survive outside of the experimental situation.

Buy U.S. Savings Bonds Regularly on the Payroll Savings Plan

OPTIONAL FORM NO. 10
(REV. 7-76)
GSA FPMR (41 CFR) 101-11.6
5010-112

OPTIONAL FORM NO. 10
MAY 1962 EDITION
GSA FPMR 101-11.6

UNITED STATES GOVERNMENT

Memorandum

TO : Herman Lewis
Senior Scientist for Recombinant DNA

DATE: 10-26-77

FROM : Mary E. Clutter
Developmental Biology Program Director

SUBJECT: Comments on the draft revision of the NIH Guidelines

In general, the revised guidelines are acceptable at this time. One problem which should receive attention is the categorization of all plant pathogens with class 2 human pathogens, thus requiring P3 EK2 containment. The Advisory Committee could not deal with this matter adequately because plant pathogens have not been classified. Until such time as they are (actually, a conference could be sponsored to deal with this), perhaps they should be treated on an individual case basis.

Buy U.S. Savings Bonds Regularly on the Payroll Savings Plan

PHARMACEUTICAL MANUFACTURERS
Association

C. JOSEPH STETLER
PRESIDENT

1155 FIFTEENTH STREET, N. W.
WASHINGTON, D. C. 20005
AREA CODE 202-296-2440

November 14, 1977

Donald S. Fredrickson, M.D.
Director
National Institutes of Health
Department of Health, Education, and Welfare
Bethesda, Md. 20014

Dear Doctor Fredrickson:

This letter is written in response to your request of October 5 for comments on the proposed revision of the NIH Guidelines for Recombinant DNA Research, published in the Federal Register, Volume 42, 187, September 27, 1977.

We are pleased to learn of the progress made in the deliberations of the Recombinant DNA Molecule Program Advisory Committee resulting in the present proposed revision. In our opinion, the revision in general reflects a more reasonable approach to the surveillance of such research and is an improvement over the original Guidelines of June 23, 1976. We are also in agreement with the observation in the new proposal that "everything we have learned tends to diminish our estimate of the risk associated with recombinant DNA in E. coli K12". We appreciate too the reasons why "the revised Guidelines continue to be deliberately restrictive, with the intent of erring on the side of caution". With additional experience in this field of research, it seems certain that some of the present restrictions will be modified and we are confident that the review mechanism now in place will assure timely consideration of such changes. The following specific comments and recommendations on the revised Guidelines are offered for your consideration.

I. Introduction

We are in agreement with the exclusion from the Guidelines of recombinant DNA molecules formed from any combination where the components are derived from genomes known to replicate within the organism used to propogate the recombinant molecules.

As was the case in the original Guidelines of June 23, 1976, the question of protection of confidential information as it affects commercial, competitive enterprise arises throughout the present revision. We recommend that an acknowledgement be made of the need for such protection and that suitable statements be included in the various sections of the Guidelines to ensure confidentiality when necessary. Under the Freedom of Information Act, research protocols, designs, data and other research results become publicly available within the context of the current and proposed Guidelines. Sections of the Guidelines where such a statement would apply include but are not limited to:

II., D., 3. - Distribution of Certified Host-Vectors
III., B., 1. c. - Lowering of Containment Levels
IV., A., paragraph 1, subsection (VI) - Submitting Information
IV., B., paragraph 5 - Minutes of Meetings

Inclusion of an appropriate statement in these sections would assure voluntary compliance by industry with all requirements of the Guidelines in addition to the physical and biological containment provisions to which we are presently committed. This inclusion would be absolutely essential if the Guidelines are ever extended by legislation or regulation to cover non-federally funded research.

II. Containment
D. Biological Containment
1. Levels of Containment
a. HV1

In general, this section is rather vague. What specifically is meant by "low potential for survival"? Also, are HV1 hosts meant to be wild type organisms or are they meant to harbor containment mutations? If HV1 host-vector systems are meant to be wild type, we propose that this section might, for example, be reworded as follows: "Hosts should be wild type species or derivatives thereof which are non-pathogenic for plants or animals and which do not contain conjugative plasmids or generalized transducing phage. Vectors should be non-conjugative plasmids or bacteriophages". If HV1 hosts are intended to harbor containment mutations, then we propose that an HVO host-vector system be defined. An HVO system could then employ a wild type non-pathogenic organism with a non-conjugative plasmid or bacteriophage vector. Experiments requiring P2+HV1 could then be carried on under P3+HVO containment. We also suggest that HVO systems should not require certification by the NIH, but approval at the institutional biohazards committee level.

3. Distribution of Certified Host-Vectors
This section should also include new certified HV1 host-vector systems.

III. Experimental Guidelines
B. Containment Guidelines for Permissible Experiments
1. Classification of Experiments Using the E. coli K-12 Host-Vector System
a. Shotgun Experiments
This section remains unnecessarily restrictive and is inconsistent with the section on lower eukaryotic DNA's. We suggest eliminating the requirement for "extensive characterization" which could inadvertently eliminate all prokaryotic DNA's other than those of E. coli, lambda and T4 from the minimum containment of P2+HV1. Surely "shotgun" experiments to clone DNA from one non-pathogenic bacterium to another cannot pose a greater potential risk than "shotgun" cloning of plant or fungal DNA into a bacterium. We propose that cloning of DNA from non-pathogenic prokaryotes requires only P2+HV1 or P1+HV2 containment. Cloning of DNA from Class 2 organisms could retain the P3+HV2 containment requirement. However, care must be taken not to inadvertently include harmless microorganisms as Class 2 agents (see Appendix A on classification of Actinomycetes), since misclassification would impose the unfortunate and unnecessary requirement of increasing both the physical and biological containment by one step. In practice, this could effectively block any recombinant DNA research with the therapeutically and economically important Streptomyces, since HV2 host-vector systems of this type will most certainly not be available for some time. Under these circumstances, the first paragraph of section III., B., a., 2. would not then be needed.

b. Plasmids, Bacteriophages and Other Viruses
There is little use in designating experimental guidelines for "permissible experiments" which cannot be met. This is the case for the classification "DNA viruses and DNA transcripts of retrovirus genomes". Furthermore, the designation of containment for this class of experiments seems disproportionately conservative. Viruses in this class belong to the NC1 category called "low-risk". In their naturally infectious forms, such viruses can be handled at what would correspond to a P2 level of containment. If we accept the Guidelines' conservative approach of assigning recombinant organisms to levels "not less

than that required for handling the most hazardous components", then a reasonable level for these experiments might be P3. Instead, they have been placed at the unobtainable level of P4 (+EK1).

To compound the problem, essentially no flexibility has been provided, for in this particular instance, a decrease of one step in physical containment (P4 to P3) requires an increase of two steps in biological containment (EK1 to EK3). This requirement again puts the experiments in the realm of the unobtainable, since no EK3 vectors are yet available (or even in the testing state).

The special concern for this category apparently relates to a situation in which DNA of an animal tumor virus is presented to a cell (presumably via E. coli K12 infection of the gut) in a form for which it has no natural resistance. Since it already seems clear that the E. coli K12 carrying a DNA insert cannot become an epidemic pathogen (especially if it is an EK2 strain) the only potential hazard is to the investigator and not to the public. Therefore, the basis for special concern and conservatism in this versus other types of viral research seems to have disappeared. Data from preliminary experiments of Martin and Rowe using the model system of polyoma virus and its highly susceptible mouse host, showed that naked polyoma virus DNA could indeed cause viral infection of mice and the highest infectivity was observed after subcutaneous injection. Impressive as this fact seems, this infectivity is still only 5×10^{-5} of the specific infectivity of the virus in its native form. One interpretation of these data is that preparing naked DNA is quite an effective method of attenuating this virus. Thus, research with DNA, or recombinant DNA including these viral genes, seems to provide an important safety advantage--at least in this particular virus-sensitive host system. It seems probable that such research would provide an even greater safety advantage when dealing with this and other viruses in a virus-insensitive host system (i.e. the hypothetical situation in which an investigator somehow becomes infected with an E. coli K12 containing viral genes). Further, the viruses in this category are not human pathogens, and they represent animal model systems which are of great biomedical importance. The current practical moratorium on recombinant DNA research with these systems does not seem to be a sound balance of benefit versus risk.

The experimental Guidelines for "viruses of plants" specify P2 + EK2 or P3 + EK1 containment. Since the two types of containment are complementary, the flexibility provided by balancing changes in physical containment with changes in biological containment is certainly reasonable. From the standpoint of the experimenter, such flexibility is also most desirable, since many more types of experiments are possible using EK1 vectors. The failure to provide a similar flexibility for other P2 + EK2 experiments, for example, shotgun experiments with DNA from mammals other than primates, or from birds appears to be inconsistent.

c. Lowering of Containment Levels for Characterized or Purified DNA Preparations and Clones

The first sentence of the last paragraph of this section should be modified in some manner to read, for example: "This institutional biohazards committee (IBC) must review and may approve such a reduction".

IV. Roles and Responsibilities

D. NIH Recombinant DNA Molecule Program Advisory Committee

The last sentence of the third paragraph of this section should be modified to take into account expertise in the field, for example: "In making recommendations for exceptions, weight will be given to scientific and societal benefits, potential risks, and to industrial experience with large-scale production of pathogenic organisms and toxic materials". This same modified statement should also appear in Section III., A., third paragraph.

We recognize that the NIH Guidelines for Recombinant DNA Research as presently constituted do not apply to research conducted in private industrial laboratories; nevertheless, the spirit and intent of the Guidelines has been, and will continue to be, followed by PMA member firms. If, at some time in the future, compliance with all provisions of the Guidelines becomes mandatory for all laboratories involved in recombinant DNA research, certain procedures in the Guidelines will pose a difficult problem in terms of patentability of new concepts and protection of proprietary interests. With the few exceptions discussed in our specific comments, compliance with all other features of the Guidelines appears reasonable.

As a general feature of the revision, then, we recommend the insertion of an acknowledgment that premature disclosure of hypotheses, protocols, designs,

data, or other research results will have a discouraging effect on research incentives. In identifying such disclosures, we differentiate between those findings which provide for greater safety and consistency in the conduct of recombinant DNA research, and those which embody the potential for commercial use through production of a desirable product. It is important not to unduly restrict the former while protecting the latter.

We are pleased to participate in your efforts to improve the Guidelines, and you have our assurance of continued cooperation and assistance in your excellent endeavor.

Sincerely yours,

C. Joseph Stetler

Enclosure

Appendix A

Fungal Agents

Actinomycetes are bacteria, not fungi, and include numerous general and an extraordinary number of species, the vast majority of which are non-pathogenic (1). For instance, Bergey's Manual of Determinative Bacteriology (1) describes 416 species and 47 subspecies of Streptomyces, while only four species are considered human pathogens (2) to avoid inadvertent classification of harmless Streptomyces and other harmless Actinomycetes of therapeutic and economic importance as Class 2 Agents, we suggest that only the pathogenic Actinomycetes be listed as Class 2 Bacterial Agents. Below is a summary of pathogenic Actinomycetes listed in references 2, 3 and 4:

Actinomyces eriksonii
Actinomyces israelii
Actinomyces bovis (bovine pathogen)
Actinomyces naeslundii
Actinomyces odontolyticus
Actinomyces suis (swine pathogen)
Actinomyces viscosus
Arachnia propionica
Dermatophilus congolensis
Nocardia asteroides
Nocardia brasiliensis
Nocardia caviae
Streptomyces niadurae
Streptomyces pelletierii
Streptomyces paraguayensis
Streptomyces somaliensis

References

1. Bergey's Manual of Determinative Bacteriology, 8th Edition. Eds. R. E. Buchanan and N. E. Gibbons. Williams and Wilkins: Baltimore. 1974.

2. Bacterial and Mycotic Infections of Man, 4th Edition. Eds. R. J. Dubos and J. G. Hirsch. Lippincott: Philadelphia. 1965.

3. Fundamentals of Medical Bacteriology and Mycology. Eds. Q. N. Myrvik, N. N. Pearsall and R. S. Weiser. Lea and Febiger: Philadelphia. 1974.

4. Actinomyces, Filamentous Bacteria. Biology and Pathogenicity. Eds. J. M. Slack and M. A. Gerencser. Burgess: Minneapolis. 1975.

American Society for Medical Technology
Office of Government Relations
1725 DeSales N.W., Suite 403
Washington, D.C. 20036
A/C 202 331-1488

November 15, 1977

Director
Office of Recombinant DNA Activities
Building 31, Room 4A52
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Sir:

The American Society for Medical Technology (ASMT) is pleased to provide the National Institutes of Health with our position on proposed revised guidelines for recombinant DNA research issued in the Federal Register on September 27, 1977.

ASMT is a national, professional organization composed of approximately 29,000 members engaged in the delivery of clinical laboratory services. The Society is composed of 50 constituent state societies in addition to the District of Columbia, which hold charters granted by the national organizations.

Our membership is made up of a variety of nonphysician categories of clinical laboratory personnel including clinical laboratory administrators, supervisors, educators, technologists, technicians, assistants, and such specialists as microbiologists, clinical chemists, hematologists, immunohematologists, cytotechnologists, histotechnologists, and nuclear medicine technologists working in hospitals, clinics (private and governmental) and research and industrial laboratories. Approximately seventy-five percent of our membership hold degrees at or above the baccalaureate level while another ten percent hold associate degrees. The remainder of the membership is composed of individuals who fall in specified categories such as students.

Our Society believes that although recombinant DNA research holds the potential of vast benefits for mankind we must also recognize the potential risks associated with such research and the real public concern that exists in this regard. On the one hand it is clear that recombinant DNA techniques hold out the promise of expanding our fundamental knowledge regarding gene function and nature, thereby providing the basis for significant progress in many areas of medical treatment. However, it is also apparent that such research may result in the possible creation of new forms of life and unknown pathogenic characteristics.

Moreover, recombinant DNA research raises some serious moral concerns with respect to modification and alteration of the human species in ethically undesirable ways.

Although ASMT strongly believes in the freedom of scientific inquiry we are also cognizant that the public must come to understand and share the belief of the scientific community that the development of DNA research under appropriate safeguards is in the best public interest. It is for this reason that ASMT takes the position that DNA research must be conducted with a full understanding of the moral implications of such scientific inquiry and under effective safety procedures which insures maximum protection to the public health and safety. In this regard, DNA research must be conducted only by competent individuals working in laboratories that are properly staffed and equipped.

It is with this philosophy in mind that our Society supports the National Institutes of Health's efforts to regulate activities involving DNA research. In evaluating the proposed NIH revised DNA guidelines the Society offers the following comments and suggestions:

1. ASMT recommends the creation of an independent regulatory enforcement mechanism to insure both compliance with established NIH guidelines and the protection of public safety. The development of such a mechanism is necessary to insure that appropriate scientific inquiry may be conducted without public suspicion that the scientific community is policing its own house without the benefit of independent review.

2. ASMT suggests the development of public educational programs to provide the information necessary to promote a general understanding of DNA research. The current lack of public understanding regarding DNA research can only serve to further perplex and confuse the public perception of such activities.

3. The Society recommends the development of uniform national standards including personnel, reporting and inspection requirements so as to insure that

minimum quality assurance standards are maintained. In that light, ASMT suggests that the adoption of previously established standards for laboratory personnel prescribed under Title VIII of the Social Security Act and the Clinical Laboratory Improvement Act of 1967 would serve to provide a consistent HEW regulatory approach.

4. ASMT recommends the acceptance of requirements for containment at the P4 and P3 level of research as previously defined in the NIH guidelines issues in July 1976. We take this position because it is clear that serious questions have yet to be satisfactorily answered regarding the manipulation of DNA molecules into various host cells which could result in converting that host cell into a dangerous pathogen, or transfer that genetic material to other healthy bacteria and transform them into pathogens.

5. ASMT suggests that the proposed change in defining recombinant DNA activities which would be limited to "novel" organisms only, fails to recognize the potential risks which may arise through the use of other host cells. The real question is not whether the organism is novel, but whether it is safe.

In summary, ASMT would hope that the NIH enact appropriate guidelines regulating recombinant DNA research, cognizant that premature lienency in restrictions over research can result in unnecessary potential risks to the public health safety.

Sincerely,

L'Nora Cross Wells

L'Nora Cross Wells
President

LCW/kay

MAILGRAM SERVICE CENTER
MIDDLETOWN, VA. 22645

western union Mailgram

2-005915C320 11/16/77 TWX MDANDERSON HOU WSHB
35 HOUSTON, TEXAS 11-16-77

DIRECTOR
NATIONAL INSTITUTES OF HEALTH
9000 ROCKVILLE PIKE
BETHESDA, MARYLAND 20014

IN RESPONSE TO PROPOSED REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH, FEDERAL REGISTER, VOL. 42, NO. 187, SEPT. 27, 1977, PART III -- SELECTED MEMBERS OF THE INSTITUTIONAL BIOHAZARDS COMMITTEE OF THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER HAVE REVIEWED THE REVISED GUIDELINES. WE ARE IN SUPPORT OF THE PROPOSED REVISIONS. THEY ALLOW FOR APPROPRIATE DOWNGRADING OF CONTAINMENT REQUIREMENTS AS APPROPRIATE VECTORS BECOME AVAILABLE BUT RETAIN ADEQUATE SAFEGUARDS FOR ALL RESEARCH INVOLVING RECOMBINANT DNA. THE ROLE OF INSTITUTIONAL BIOHAZARDS COMMITTEES IN REVIEW OF FACILITIES, PERSONNEL, AND PROCEDURES SHOULD BE RETAINED. WE URGE EARLY ADOPTION OF THE REVISED GUIDELINES.
ROBERT C. MICKEY, M.D.
EXECUTIVE VICE PRESIDENT AND DIRECTOR
THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER
HOUSTON, TEXAS 77030

10:04 EST

MGMCOMP MGM

The University of Michigan

COLLEGE OF ENGINEERING
DEPARTMENT OF HUMANITIES

525 EAST UNIVERSITY
ANN ARBOR, MICHIGAN 48109

(313) 764-1420

November 18, 1977

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I enclose some brief comments on proposed revisions to the guidelines for recombinant DNA research, which would have the effect of lowering containment levels.

1. I see no sound scientific reasons for lowering containment levels at this point. Much of the data cited as a reason for relaxation is unpublished, and has not received the independent criticism and testing that is necessary before the data can be said to have achieved the status of sound scientific fact.

Discussions at the Falmouth Workshop on assessment of the potential risks in this field demonstrated that uncertainty and sharp disagreement continue to surround critical aspects of the risks, including (a) the possibility of transfer of recombinant DNA from "safe" bacterial hosts to other strains of the host and other bacterial species; (b) the possibility of triggering autoimmune responses in humans and animals; (c) the possibility of conferring a selective advantage to host bacteria through routine use of antibiotic resistance genes as "markers"; (d) the possibility of altering properties of viruses, such as infectivity or host range; (e) the implications of modifying plant and animal species.

For discussions of these areas, I refer you to the letters sent to you by Dr. Bruce Levin, Dr. Jonathan King, and Dr. Richard Goldstein, the analysis of the new data made by Dr. Burke Zimmerman for the House Subcommittee on Health and the Environment, and the transcript of the Falmouth conference, if available.

The use of unpublished scientific opinions that have not been independently tested and verified to support relaxation of the guidelines represents an unfortunate departure from accepted canons of scientific procedure. It is unthinkable that unverified data would be tolerated as a basis for the exploration of space or for the construction of buildings, bridges or tunnels. No more should such data be used in this case, where human lives may equally be at risk.

2. Relaxation of present standards of containment could easily be taken as a signal to practitioners of gene splicing that the risks are now minimal. Relaxation is also a signal to other countries to drop their standards. The caution urged three years ago may well be thrown to the winds. Yet our ignorance of the implications of many fundamental aspects of gene splicing is as complete now as it was then.

3. At the hearings held this month by the Senate Subcommittee on Science, Technology, and Space, there appeared to be almost unanimous agreement that regulation of this field is necessary. Until Congress passes legislation and new regulations are promulgated, interim standards should not be lowered. Lowering of standards creates, de facto, a policy of progressive relaxation which could be difficult to reverse. If anything, the standards should be raised. I see no reason to change my view stated in earlier letters, that the present guidelines, which permit rapid expansion of this field, in no way guarantee containment of the potentially hazardous organisms to be manufactured.

Sincerely yours,

Susan Wright

Susan Wright

SPW:vw

The Connecticut Agricultural Experiment Station

123 HUNTINGTON STREET BOX 1106 NEW HAVEN, CONN. 06504 (203) 787-7421

Founded 1875 *Putting science to work for society*

18 November 1977

Dr. Donald S. Fredrickson
Dept. of Health, Education & Welfare
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

Two aspects of the revised guidelines are of some concern to plant scientists:

(i) The introduction refers to the fact that the Guidelines "pertain only to novel recombinant DNAs...from different species not known to exchange chromosomal DNA by natural physiological processes". They go on to refer to a list of combinations of DNAs not considered novel. I believe that the word "chromosomal" should be eliminated. Prokaryotes that exchange plasmid DNA surely also exchange chromosomal DNA that happens to be part of the plasmid. I do not see the need for formal proof of this for each pair to be included in a list.

Agrobacterium tumefaciens offers one of the most promising systems for introducing foreign DNA into plants. It exchanges plasmids with E. coli, Rhizobium and other gram-negative bacteria. I would interpret the revised guidelines to list A. tumefaciens x E. coli, and A. tumefaciens x R. trifolii as exchangers. This would allow important work with E. coli K12 clones of A. tumefaciens plasmid DNA to proceed without any restriction instead of P2 + EK2 presently required.

However if a less liberal interpretation requires documentation of exchange of chromosomal DNA between the strains to be employed then, in the meantime, containment will be severely increased as explained in my second point.

(ii) The revised guidelines require P2 + EK2 or P3 + EK1 for non-exchanging bacteria with DNAs that are not extensively characterised. However, plant pathogens are equated with Class 2 and require P3 + EK2 (P49602 Col. 1. line 29). This is a mistake. Although there is still no risk classification for plant pathogens beyond endemic vs. exotic species there is little reason to equate plant pathogenic bacteria with class 2 agents. American scientists working with A. tumefaciens for example would be greatly hampered by P3 + EK2. I suggest that the words "and plant pathogens" be deleted on this line. This

would restore containment to P2 + EK2 for shotgun experiments, the level that obtains at the present time and which is also required for plant virus DNA.

Sincerely,

Peter R. Day, Head
Department of Genetics

PRD/ebb

INTERNATIONAL PAPER COMPANY

TUXEDO PARK, N.Y. 10987, PHONE 914 351-2101

CORPORATE R & D DIVISION

November 21, 1977

Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Sir:

At present, the NIH Guidelines for Recombinant DNA Research do not apply to privately funded research on this subject, but proposed legislation indicates that these guidelines may become the basis for future regulation. Even though these Guidelines do not presently govern activities in our laboratories, it is not our intent to initiate efforts that might be considered irresponsible, and we desire to keep any efforts we might initiate within the limits imposed by these Guidelines so that the disruption of our programs by pending regulation can be minimized.

In general, my response to proposed revision is favorable. The emphasis is understandably focused on operational systems in bacteria and mammalian cells. Our interest is on host-vector systems by which recombinant DNA techniques can be extended to plants. To the best of my knowledge, no such systems are available. My purpose in writing is neither to endorse nor denounce any particular provision in the proposed revision, but to raise certain questions regarding intent and interpretation.

Novel Recombinant DNAs. If one assumes that recombinant DNA formed from species of plants capable of producing viable interspecific hybrids (i.e. different species known to exchange chromosomal DNA by natural physiological processes) are not novel recombinant DNAs, meaningful efforts in development of host-vector systems employing plant organelle genomes as vectors can be initiated with materials not regulated under the proposed revisions. Furthermore, if recombinant DNAs formed from plant viruses and DNA from plants with which the viral host can hybridize are propagated in normal viral host (i.e., all components are derived from genomes known to replicate within the organism used to propagate the recombinant DNA) are not considered to be novel recombinant DNAs, the use of plant viruses as vectors can be investigated using materials not regulated by the proposed revision of the Guidelines. These two

assumptions seem to be consistent with the wording of the Introduction of the proposed revision, but the proposed revision also requires specific exclusion of recombinant DNAs not considered novel. My interpretations and the required exclusions would place a nearly impossible burden on the Director and the Recombinant DNA Molecular Program Advisory Committee if such a list of combinations of DNAs is actually prepared.

Certification of Host-Vector Systems. To explore applications of recombinant DNA technology in plants requires the development of useful host-vector systems. The vector concept implies a genetic element that can transmit a fragment of foreign DNA and direct its replication. To develop a host-vector system for novel recombinant DNA, the proposed revision requires one to determine with which organism the host normally exchanges genetic information, with which organisms the vector exchanges genetic information, and what sort of information is exchanged before that host-vector system can be employed in recombinant DNA research. These tasks required for certification will be simplified and the answers determined with greater precision if recombinant DNAs not considered novel (according to the previous discussion) are employed and results analyzed with molecular probes. Furthermore, the section of the proposed revision of the Environmental Guidelines dealing with plant host-vector systems allows certain vectors to be employed for transfer of recombinant DNA to host plant material under P2 and P3 levels of containment. In the same section, the proposed revision provides for a reduction of containment level if hosts such as undifferentiated plant cells in culture are employed. I assume that the studies contemplated in these sections are restricted to certified host-vector systems.

Forbidden Experiments. Under the section of the Experimental Guidelines dealing with plant host-vector systems, "whole plants or plant parts that cannot be adequately contained" are restricted. I cannot determine whether the intent is to forbid experiments with whole plants or to forbid experiments with whole plants that cannot be adequately contained. I assume the latter interpretation is consistent with the intent because elsewhere in the same section, the quidelines implies that plant parts or whole mature plants of small species (e.g., Arabidopsis) can be adequately contained. This interpretation raises yet another question. No matter how large the species in question may normally become, it can be used experimentally as a small plantlet or seedling. I raise this question because embryogenesis from suspension culture is a rapidly evolving technique that might usefully be employed to determine the effect of recombinant DNA on plant hosts. The normal size of the plant species is relatively unimportant because the experiment can be terminated at any time physical requirements for containment dictate.

Modified Viruses. In much of the work one might presently contemplate, the vector would be a recombinant DNA formed from an infectious viral genome. I assume that such a vector would be considered a modified virus.

These points have been communicated with a constructive intent. If further clarification is necessary or if I can be of further assistance, please let me know.

Sincerely,

William W. Eudy
Manager - Forest Sciences

WWE:daw

THE JOHNS HOPKINS UNIVERSITY
BALTIMORE, MARYLAND 21218

MERGENTHALER LABORATORY
FOR BIOLOGY

November 24, 1977

Dr. Donald Fredrickson
Director, National Institutes of Health
c/o Office of Recombinant DNA Activities
National Institute of Allergy and Infectious Diseases
NIH
Bethesda, Maryland 20014

Dear Dr. Fredrickson,

As a scientist having worked in microbiology and in bacterial genetics for some 25 years, I would like to make some comments on the Proposed Revised Guidelines on Recombinant DNA Research (Federal Register, Vol. 42, No. 187 -- Tues., Sept. 27, 1977, pp. 49596-49609) and on closely related matters. I request that these comments be made available to the Advisory Committee for consideration in its deliberations beginning December 15th.

(1) The Proposed Guidelines should be strengthened with regard to provisions for the handling of recombinant DNA molecules once separated from their hosts or vectors (Sec. III-B-5). Most of the recombinant DNA molecules are going to be small, circular replicons that can easily invade, and replicate in, bacteria ubiquitous to the environment. It is utterly absurd to specify P1 containment for nuclease-protected, small circular molecules while, at the same time, carefully clearing "safer" cloning vehicles! Instead of P1 classification, DNA molecules free of vectors should be classified at one step in physical containment lower than that specified for the DNA-vector-host complex itself. AFTER the DNA of interest has been separated from the replicon (AND made linear), ONLY THEN should the DNA be allowed a second-step lower classification, but only after clearance with the local Biohazards Committee. I do not think that discussions of recombinant DNA have adequately addressed this point, nor is either version of the Guidelines truly cognizant of this quaint "loophole".

(2) All research and production involving biochemically synthesized recombinant DNA molecules in the U.S.A. should be made subject to NIH Guidelines and reporting. The Guidelines should be clearly applicable to such research wherever conducted and regardless of its auspices, public or private. I believe strongly that new legislation will be required to make this ruling effective, all-inclusive, unhindered by minor and obscure prior legislation, non-subject to obstructive legal action whether pertinent or not, and clearly understandable and enforceable. Laws have indirect value in changing attitudes (and the attitudes of many scientists do need changing), as perhaps best seen in recent years in Civil Rights legislation. It is not true that "if people are going to break codes of practice or codes of honor in this area, they will break the laws" (p. 520, "Recombinant Molecules" 1977). Scientists working in the field know that the "code" already has been broken a number of times or the rules stretched almost beyond belief. The Guidelines need the force of law not only to implement their extension beyond NIH-funded research but, also, to encourage strict compliance within a more select segment of the scientific community. No "sunset clause" is necessary or realistic. Science will not find all the answers "tomorrow"; the new, proposed Guidelines are highly adaptable.

(3) Legislation in (2) should lay out standards for strict, expert, and unannounced monitering both of public and of private institutions, including commercial firms. The legislation should provide authorization for a bucet to include record-keeping and monitering activities. The legislation should lay out formal penalties, including the option for criminal penalties in cases where there is severe and blatant disregard for law and public safety.

Monitering of numerous sample laboratories should include close checks on vectors and host strains. Even the experts don't know where one of the most widely used DNA vehicles originated (Cohen, S.N. and Chang, A.C.Y. 1977 J. Bact. 132:734-737), and the literature is replete in microbial genetics with strain substitutions, lost genetic markers, etc., etc. And, by many of the better, more experienced research scientists.

Monitering of a different kind should be performed right now, namely an in-depth investigation of perhaps two laboratories (including personnel, families, environment, etc.) that have been working with recombinant DNA for some time. This investigation should be carried out by an unbiased and highly expert research team that knows its epidemiology, bacteriolgy (including familiarity with obligate anaerobes such as bacteroides, the fusiforms, etc.), and modern RNA/DNA methodology. For example, does laboratory Pseudomonas carry Xenopus 5S or ribosomal RNA, or any SV40 genes? It is clear that different DNA segments soliced into circular or potentially circular (lambda) DNA molecules have various survival values, but right now we have absolutely no idea what has already happened and, thus, little basis for projection (see Richmond and Lederberg in "Recombinant Molecules" 1977).

(4) The Director and the Recombinant DNA Molecule Program AdvisoryCommittee should proceed with extreme caution in exercising exclusions to "novel recombinant DNA" designation. No blanket exclusions (eg. "Enteric bacteria") should be made. In fact, no exclusions of particular species should be made. Great heterogeneity is to be found even among natural isolates of E. coli (So and Falkow 1977 " Recombinant Molecules"). Plasmid transfer is extremely wide among bacterial "species", "genera", "families" and even among "families" classified in different Parts of "Bergey's Manual"(Sanderson, K.E. 1976 Ann. Rev. Micro. 30:327-349; Jones, D, Sneath, P.H.A. 1970 Bact. Rev. 34:40-81) in spite of minimal effort and only moderate technology so far used to detect such transfers. Therefore, genetic exchange in Nature cannot be a criterion for exclusion. I think it entirely reasonable at this point to classify ALL organisms under the Proposed Guidelines and exclude, for example, E. coli K12 DNA in E.coli K12. The revised Guidelines have provisions for exclusions in specific instances with well-defined DNA molecules that seem to cover basic scientific needs.

I hope that the Committee and the Director give attention to the above four points. In closing, I want to point out that the First Amendment is not an issue. Publishing IDEAS is a far-cry from actually making recombinant molecules. Recombinant DNA technology affords very obvious prospects for misue which, unfortunately, many non-microbiologists do not seem able to visualize or, at least, do not want to recognize. I suggest that nationwide promulgation of the Guidelines be followed by Executive Order, in follow-up of President Nixon's renouncement of development and stockpiling of biological warfare agents (Nov. 25, 1969), and, thereafter, international agreements be made to help assure that the new technology will be put to beneficial uses insofar as possible. Finally, let me state that man's experiments are NOT Nature's experiments. Construction of a recombinant molecule by a sequence of steps, sometimes six steps each with a "probability" of 10^{-6}, and selective growth of the output molecule cannot be called "Nature's experiment...it's happening all the time"!

Respectfully yours,

Philip E. Hartman
William D. Gill Professor in Biology

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOCHEMISTRY

PAUL BERG
Jack, Lulu and Sam Willson
Professor of Biochemistry

December 5, 1977

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Building 1, Rcom 124
Bethesda, MD 20014

Dear Don,

Last week Bernie Talbot asked me to try to rewrite the definition of recombinant DNA molecules for the revised version of the Guidelines, so as to include molecules containing synthetic DNA sequences. He also asked me to indicate my views on what level of containment could be recommended for experiments with such synthetic DNA segments.

Enclosed is what I came up with. Seems simple enough but perhaps I have overlooked something. Nevertheless, it should be useful as it is or in any amended form.

Good luck in your efforts for this round of revisions.

With best regards,

Sincerely yours,

Paul

PB:ab
c.c. B. Talbot

Proposed Inclusions in Revised Guidelines to Cover Recombinant DNA Experimentation with Synthetic DNA Segments. Paul Berg

1) To replace paragraph 1 Page I-1 (Technical Bulletin on Recombinant DNA).

I. Introduction-

The purpose of these Guidelines is to establish procedures for constructing and handling organisms and viruses containing recombinant DNA molecules. Recombinant DNA molecules are defined as molecules which have been constructed outside of living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate or be integrated into the genome of a living cell. However, the recommendations contained herein pertain only to organisms and viruses that contain "novel" recombinant DNAs where the word "novel" applies to molecules containing a) natural DNA segments or reverse trans. ipts from species not known to exchange DNA by normal physiological processes or b) synthetic DNA segments whose nucleotide sequence can or might be expressed as a polynucleotide or polypeptide that is not known to be made in the chosen host cells. The Director of the NIH, with the advice of the Recombinant DNA Molecule Advisory Committee, shall prepare a list of those combinations of DNAs (viral, extrachromosomal or chromosomal) which are not considered novel for this purpose and are, therefore, not covered by these Guidelines. In general recombinant DNA molecules formed from any combination of DNAs will not be considered novel when all the components are derived from genomes known to replicate within the organism used to propagate the recombinant DNA.(1)

2) To be inserted on page III-28 as item 5;and change "Handling of Recombinant DNA Molecules" to item 6.

5. Synthetic DNAs-

The containment conditions recommended for handling organisms containing synthetic DNA molecules are those described for propagating the natural DNA segments they are intended to emulate.

If the synthetic DNA sequence codes for a harmless product normally made in a prokaryote (one not known to exchange genetic information with E. coli) a eukaryote, or their plasmids, viruses or organelles, may use the lowest combination of physical and biological containment conditions recommended for the corresponding purified natural DNA segment. (Perhaps some examples here would be useful).

If the synthetic DNA segment can or might yield a potentially harmful polynucleotide or polypeptide (e.g. a toxin or a pharmacologically disruptive agent) the containment conditions should be the same as would be used for propagating the purified natural DNA counterpart. (Perhaps some examples here could also be included.)

If the synthetic DNA segment is not expressed as a polynucleotide or polypeptide product,or their products have no natural counterparts,the organisms containing the recombinant DNA molecules are exempt from consideration by these Guidelines.

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TO THE DIRECTOR DR. D. FREDRICKSON

FROM EMBO STANDING ADVISORY COMMITTEE ON RECOMBINANT DNA RESEARCH

DRAFT REPORT ON REVISED NIH GUIDELINES

PROPOSED REVISIONS TO THE NIH GUIDELINES

GENERAL COMMENTS

IN JUNE 1976 THE NIH OF THE USA ISSUED GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES, IT BEING UNDERSTOOD THAT PERIODIC REVISIONS WOULD BE MADE TO THE GUIDELINS IN THE LIGHT OF FURTHER KNOWLEDGE AND EXPERIENCE. DURING THE SUMMER OF 1977 THE NIH ADVISORY COMMITTEE BEGAN THE PROCESS OF REVISING THE GUIDELINES AND PROPOSED REVISED GUIDELINES WERE PUBLISHED IN THE FIRST ISSUE OF THE NIH'S RECOMBINANT DNA TECHNICAL BULLETIN. THE EMBO COMMITTEE HAS DISCUSSED IN SOME DETAIL THE REVISIONS THAT ARE PROPOSED AND HAS REACHED THE CONCLUSIONS REPORTED IN THE FOLLOWING PARAGRAPHS. THE EMBO COMMITTEE WILL CONVEY BY LETTER

ITS COMMENTS TO THE NIH ADVISORY COMMITTEE AND TO THE DIRECTOR OF THE NIH.

THE REVISIONS PROPOSED REPRESENT A SIGNIFICANT RELAXATION OF THE CONTAINMENT CONDITIONS REQUIRED FOR MOST CLASSES OF RECOMBINANT DNA EXPERIMENTS AND THEY ALSO PROVIDE GREATER FLEXIBILITY IN ATTAINING PARTICULAR LEVELS OF PHYSICAL CONTAINMENT. THE EMBO COMMITTEE CONSIDERS THAT THESE CHANGES ARE JUSTIFIED FOR THE REASONS DISCUSSED BELOW AND SUGGESTS THAT THE LEVELS OF CONTAINMENT FOR CERTAIN CLASSES OF EXPERIMENTS SHOULD INDEED BE REDUCED SOMEWHAT FURTHER THAN IS PROPOSED BY THE NIH ADVISORY COMMITTEE.

THE PRINCIPAL REASONS FOR RECOMMENDING SIGNIFICANT RELAXATION OF THE CONTAINMENT MEASURES FOR RECOMBINANT DNA EXPERIMENTS IN GENERAL, AND THOSE WHICH INVOLVE THE USE OF E.COLI K12 AS THE HOST ORGANISM IN PARTICULAR, ARE TWO- FOLD. FIRST, WE ARE BECOMING INCREASINGLY AWARE THAT IN NATURE THERE IS A CONSIDERABLE POTENTIAL FOR EXCHANGE OF GENES THAT DOES NOT DEPEND UPON EXTENSIVE HOMOLOGIES BETWEEN DNA SEQUENCES. EXCHANGE OF GENES BETWEEN BACTERIA AND HIGHER PLANTS, FOR EXAMPLE, HAS NOW BEEN SHOWN TO OCCUR IN NATURE. MOREOVER, IN THE LABORATORY IT HAS BEEN SHOWN THAT E.COLI PRODUCING RESTRICTION ENZYME NOT ONLY TAKE UP DNA BUT ALSO INCORPORATE IT INTO THEIR CHROMOSOMES BY AN IN VIVO PROCESS THAT INVOLVES THE ENDOGENOUS RESTRICTION ENZYMES. IN SHORT THE SORTS OF GENE COMBINATIONS THAT CAN BE GENERATED IN THE LABORATORY BY IN VITRO RECOMBINANT DNA METHODS

CAN APPARENTLY ALSO BE GENERATED NATURALL Y IN VIVO ALBEIT ON A LESSER SCALE. SECOND, NEW DATA ABOUT THE BIOLOGY OF E.COLIK12 INDICATE THAT (1) E.COLI K12 DOES NOT COLONISE THE HUMAN GUT (2) E.COLI IS NOT PATHOGENIC (3) E.COLI K12 CANNOT BE MADE COMMUNICABLE OR PATHOGENIC EVEN BY INTRODUCING GENES FOR TOXINS AND OTHER PATHOGENIC PROPERTIES FROM OTHER STRAINS OF E.COLI BY STANDARD GENETIC METHODS (4) THE PROBABILITY OF TRANSMISSION IN THE ANIMAL GUT OF NON-CONJUGATIVE PLASMID VECTORS FROM AN E.COLI K12 HOST TO SOME OTHER BACTERIUM IS LESS THAN 10 -16 PER BACTERIUM PER DAY. IN SHORT E.COLI K12 IS SO GENETICALLY DEFECTIVE THAT IT IS INCAPABLE OF BECOMING A PATHOGEN. THE STRAINS OF E.COLI K12 THAT HAVE BEEN FURTHER DISABLED BY THE INTRODUCTION IN THE LABORATORY OF MANY MUTATIONS WHICH FURTHER RESTRICT THE CONDITIONS IN WHICH THE ORGANISM CAN SURVIVE (BIOLOGICALLY CONTAINED E.COLI K12: EK2 HOSTS) PRESENT NO THREAT TO MAN OR HIS ENVIRONMENT.

WHEN THE ORIGINAL GUIDELINES WERE DRAWN UP THIS INFORMATION WAS NOT AVAILABLE, AT THAT TIME IT WAS SUGGESTED BY SOME THAT E.COLI K12 MIGHT BE READILY CONVERTED INTO A PATHOGEN BY THE INTRODUCTION OF FOREIGN DNA. MOREOVER, NATURAL BARRIERS TO THE EXCHANGE OF GENETIC MATERIAL BETWEEN SPECIES SEEMED GREATER THAN WE NOW KNOW THEM TO BE. THE NEW EVIDENCE DISPELS MANY OF THESE FEARS AND SO THE CONTAINMENT MEASURES INITIALY AND PRESENTLY REQUIRED ARE NOW RECOGNISED AS BEING TOO STRINGENT AND SHOULD BE RELAXED.

SPECIFIC COMMENTS

PHYSICAL CONTAINMENT SPECIFICATIONS

THE EMBO COMMITTEE WELCOMES THE MORE DETAILED DESCRIPTIONS OF PHYSICAL CONTAINMENT MEASURES GIVEN IN THE REVISED NIH GUIDELINES, NOTING THAT THEY ARE SUBSTANTIALLY IN ACCORD WITH THE PROPOSALS AND RECOMMENDATIONS OF A JOINT NIH-EMBO WORKSHOP HELD IN MARCH (ANNEX 2). THE SEPARATE DESCRIPTION OF THE THREE COMPONENTS OF EACH LEVEL OF PHYSICAL CONTAINMENT, NAMELY THE LABORATORY DESIGN, THE LABORATORY PRACTICES AND THE SPECIAL CONTAINMENT EQUIPMENT, IS PARTICULARLY USEFUL. CONCERNING THESE SPECIFICATIONS THE EMBO COMMITEEE HAS ONLY A FEW COMMENTS: (A) IT BELIEVES THAT MOUTH PIPETTING SHOULD BE PROHIBITED IN THE P1 LABORATORY, AS IT IS PROHIBITED IN P2-P4 LABORATORIES, AND IT RECOMMENDS THAT SIMPLE AIR EXHAUST CABINETS, SUCH AS A CONVENTIONAL FUME CUPBOARD, BE USED IN THE P1 LABORATORYFOR THOSE MANIPULATIONS LIKELY TO PRODUCE LARGE AMOUNTS OF AEROSOLS, (B) IN THE SPECIFICATION OF THE P3 LABORATORY, WHICH MAY BE EQUIPPED WITH RUNNING WATE,, OR LOCATED BENEATH OR NEXT TO LABORATORIES WITH RUNNING WATER, PRECAUTIONS AGAINST THE CONSEQUENCES OF FLOODING OR CONTAMINATION OF THE MAINS WATER SUPPLY ARE NOT DISCUSSED.

PROPOSED 'TRADE OFFS'

THE PROPOSALS TO INCREASE THE FLEXIBILITY OF CONTAINMENT MEASURES BY ALLOWING CERTAIN ALTERNATIVE COMBINATIONS OF SAFEGUARDS ARE WELCOMED BY THE EMBO COMMITTEE. THE EMBO COMMITTEE SUPPORTS THE

PRINCIPLE THAT, FOR CERTAIN EXPERIMENTS, IF BIOLOGICAL CONTAINMENT IS INCREASED BY ONE STEP A REDUCTION OF ONE STEP IN SPECIAL CONTAINMENT EQUIPMENT CAN BE ALLOWED, AND CONVERSELY, THAT BIOLOGICAL CONTAINMENT CAN BE REDUCED BY ONE STEP WHEN THE PHYSICAL CONTAINMENT EQUIPMENT IS INCREASED BY ONE STEP. THESE CHANGES ARE ENVISAGED BY THE NIH COMMITTEE FOR P3 AND P4 PHYSICAL CONTAINMENT AND FOR EK1 AND EK2 BIOLOGICAL CONTAINMENT. THE EMBO COMMITTEE PROPOSES THAT THEY BE EXTENDED TO P2 AND P3 PHYSICAL CONTAINMENT SUCH THAT A COMBINATION OF A LABORATORY DESIGNED TO P2 SPECIFICATIONS WITH A CLASS 3 CABINET EXHAUSTING TO THE OUTSIDE AIR, BE CONSIDERED EQUIVALENT TO A LABORATORY DESIGNED AND EQUIPED TO P3 SPECIFICATIONS.

CATEGORIZATION OF SAFETY MEASURES FOR PARTICULAR CLASSES OF EXPERIMENTS

THE EMBO COMMITTEE TAKING INTO CONSIDERATION THE NEW DATA MENTIONED ABOVE IN PARAGRAPH 3.3, BELIEVES THAT FOR 'SHOTGUN' EXPERIMENTS INVOLVING TISSUE FROM HEALTHY ORGANISMS THE BASIC COMBINATIONS OF BIOLOGICAL AND PHYSICAL CONTAINMENT SHOULD BE THOSE SHOWN IN COLUMN 1 OF TABLE1. FOR COMPARISON COLUMN 2 OF TABLE 1 SHOWS THE CONTAINMENT COMBINATIONS PROPOSED IN THE REVISED NIH GUIDELINES. THE EMBO COMMITEE'S RECOMMENDATIONS RELAX THE CONTAINMENT COMBINATIONS FURTHER THAN THE PROPOSALS OF THE NIH ADVISORY COMMITTEE. THE FORMER DOES NOT BELIEVE PRIMATE DNA TO BE MORE HAZARDOUS THAN THE DNA OF OTHER MAMMALS AND BIRDS, AND NONE OF THE EXISTING

EUROPEAN GUIDELINES MAKE A DISTINCTION BETWEEN PRIMATE AND OTHER MAMMALIAN DNA SO LONG AS IT IS OBTAINED FROM NORMAL HEALTHY TISSUE.

TABLE 1	COLUMN 1	COLUMN 2
SOURCE OF DNA"	EMBO STANDING ADVISORY COMMITTEE'S PROPOSALS	NIH ADVISORY COMMITTEE'S PROPOSALS
ALL MAMMALS AND BIRDS	P2 " EK2	PRIMATES P3 " EK2
OTHERS	P2 " EK2	
ALL OTHER EUKARYOTES	P1 " EK2 P2 " EK1	INVERTEBRATES P1"EK2 OR P2 " EK1 PLANTS P2 " EK1 OR P1 " EK2
PROKARYOTES	P1 " EK1	P2 " EK2 (NOT WELL CHARACTERIZED P1 " EK2 (WELL CHARACTERIZED

"APPLIES ONLY TO NON-PATHOGENIC SPECIES, TO DNA FROM NORMAL HEALTHY TISSUE OF SUCH SPECIES, AND TO E. COLI K12 HOST VECTOR SYSTEMS.

THE EMBC COMMITTEE BELIEVES THAT DNA OF AMPHIBIA, REPTILES AND FISH POSES LESS OF A CONJECTURAL HAZARD THAN THAT OF MAMMALS AND PRIMATES AND, THEREFORE, REQUIRES A LOWER LEVEL OF CONTAINMENT

THE EMBO COMMITTEE HAS NOT DISCUSSED IN DETAIL THE CONTAINMENT CONDITIONS FOR EXPERIMENTS WITH THE DNA OF ORGANISMS, OF THE VARIOUS PHYLOGENETIC CLASSES, THAT ARE PATHOGENIC OR ARE THE HOSTS OF PATHOGENS. THE CONTAINMENT CONDITIONS FOR THESE, AND FOR EXPERIMENTS WITH DNA FROM PATHOLOGICAL TISSUES FROM ANY ORGANISM SHOULD BE DECIDED CASE BY CASE, TAKING INTO CONSIDERATION FACTORS SUCH AS THE PRODUCTION BY THE PATHOGEN OF A POLYPEPTIDE OR NON-POLYPEPTIDE TOXIN, THE HOST RANGE OF THE PATHOGEN, THE PRECISE NATURE OF THE PATHOLOGICAL TISSUE AND THE DISEASE, ETC. IRRESPECTIVE OF THE TAXONOMIC POSITION OF THE DONOR ORGANISM, ALL EXPERIMENTS INVOLVING THE DNA OF PATHOGENS OR PATHOLOGICAL TISSUES SHOULD BE REFERRED TO THE NATIONAL COMMITTEE BEFORE THEY ARE STARTED. IN GENERAL THE EMBO COMMITTEE RECOMMENDS THAT IN THESE CASES EITHER THE PHYSICAL OR THE BIOLOGICAL CONTAINMENT MEASURES BE INCREASED BY AT LEAST ONE STEP.

PROHIBITED EXPERIMENTS

THE EMBO COMMITTEE ACCEPTS IN PRINCIPLE THE PROPOSAL XADE IN THE NIH GUIDELINES THAT CERTAIN RECOMBINANT DNA EXPERIMENTS SHOULD NOT AT PRESENT BE INITIATED, HOWEVER, THE LISTS OF PARTICULAR

PATHOGENIC ORGANISMS THAT FALL UNDER THE PROHIBITION, IN PARTICULARE AGENTS IN CLASS 5 OF THE CLASSIFICATION OF ETIOLOGIC AGENTS ON THE BASIS OF HAZARD, MAY NOT NECESSARILY BE APPROPRIATE FOR ALL EUROPEAN COUNTRIES. FOR EXAMPLE SEVERAL VIRUSES OF DOMESTIC ANIMALS THAT ARE NOT PRESENT IN NORTH AMERICA ARE ENDEMIC IN PARTS OF EUROPE, AND IT WOULD BE UNREASONABLE TO ABSOLUTELY PROHIBIT WORKING WITH THEM IN THOSE COUNTRIES. THE DECISION AS TO WHICH PATHOGENIC ORGANISMS SHOULD BE CLASSIFIED AS TOO DANGEROUS TO USE MUST BE THE RESPONSIBILITY OF NATIONAL OR REGIONAL AUTHORITIES.

CLONING VIRAL DNA

THE EMBO COMMITTEE BELIEVES THAT THE CONTAINMENT CATEGORIZATION OF EXPERIMENTS WITH ANIMAL VIRAL DNAS WHICH IS PROPOSED BY THE NIH ADVISORY COMMITTEE IS TOO INDISCRIMINATE AND EXCESSIVELY STRINGENT CONSIDERING THE PROPOSED CLASSIFICATION OF EXPERIMENTS WITH OTHER CLASSES OF DNA AND THE LONGSTANDING, ACCEPTED SAFETY PRECAUTIONS FOR HANDLING INTACT VIRUS PARTICLES AND VIRAL NUCLEIC ACIDS. THE EMBO COMMITTEE BELIEVES THAT THERE IS NO JUSTIFICATION FOR PLACING SHOTGUN EXPERIMENTS WITH DNA OF ALL VIRUSES OF WARM BLOODED AND COLD BLOODED ANIMALS IN ONE SINGLE CATEGORY (P4 " EK1 OR P3 " EK3) BECAUSE THEIR HOST RANGE, VIRULENCE AND PATHOGENICITY VARY MARKEDLY. IT SEEMS UNREASONABLE TO REQUIRE EQUALLY STRINGENT CONTAINMENT CONDITIONS FOR EXAMPLE FOR DNA OF MOUSE MINUTE VIRUS ON THE ONE HAND AND FELINE LEUKAEMIA VIRUS AND MASON PFIZER MONKEY VIRUS ON THE OTHER. THE EMBO COMMITTEE

PROPOSES THAT IT WOULD BE MORE REASONABLE EITHER TO CONSIDER EXPERIMENTS WITH VIRAL DNA ON A CASE BY CASE BASIS OR TO PRODUCE A DETAILED SET OF RECOMMENDED CATEGORIES FOR EXPERIMENTS WITH SPECIFIC VIRAL DNAS. SINCE THE LATTER IS BEYOND ITS COMPETENCE THE EMBO COMMITTEE HOPES IN THE NEAR FUTURE TO ESTABLISH AN AD HOC INTERNATIONAL GROUP OF VIROLOGISTS TO DRAW UP SUCH PROPOSALS.

VIRUSES AS VECTORS

IN EXPERIMENTS INVOLVING THE INTRODUCTION OF FOREIGN DNA INTO CULTURED CELLS OF ANIMALS USING DNA VIRUSES AS VECTORS, BIOLOGICAL CONTAINMENT IS ASSURED BY THE VERY RESTRICTED PERMISSIVE CONDITIONS FOR THE HOST CELLS, THE ONLY ROUTES BY WHICH THE RECOMBINANT MOLECULE MIGHT ESCAPE ARE BY CHANCE INFECTION OF A CONTAMINATING MICROORGANISM OR WITHIN A VIRAL CAPSID AND THE SIZE OF THE RECOMBINANT MOLECULE MAY WELL PRECLUDE ITS ENCAPSIDATION. THE EMBO COMMITTEE BELIEVES THAT THE CATEGORIES OF PHYSICAL CONTAINMENT REQUIRED SHOULD DEPEND PRINCIPALLY UPON THE TAXONOMIC RELATIONSHIP BETWEEN THE DONOR OF THE DNA BEING CLONED AND THE NATURAL HOST SPECIES OF THE VECTOR VIRUS.

A DETAILED SET OF CATEGORIES BASED UPON THE FOLLOWING PRINCIPLES IS CALLED FOR:

DONOR DNA FROM A SPECIES THAT IS

A HOST FOR THE VECTOR - LOW LEVEL PHYSICAL CONTAINMENT

DONOR DNA FROM AN EUKARYOTE NOT SUSCEPTIBLE TO THE VECTOR - MEDIUM LEVEL PHYSICAL CONTAINMENT

DONOR DNA FROM A PROKARYOTE - HIGHER LEVEL PHYSICAL CONTAINMENT

FOR EXAMPLE CLONING OF MOUSE DNA USING POLYOMA VIRUS AS A VECTOR AND MOUSE CELLS AS HOST SHOULD NOT REQUIRE PRECAUTIONS MORE STRINGENT THAN THOSE ROUTINELY USED FOR MANY YEARS IN LABORATORIES STUDYING POLYOMA VIRUS INFECTION OF MOUSE CELLS AND MICE.

THE EMBO COMMITTEE FINDS THE PROPOSALS FOR THIS CLASS OF EXPERIMENTS IN THE REVISED NIH GUIDELINES NOT SUFFICIENTLY DISCRIMINATING BECAUSE THEY WOULD IMPOSE UNNECESSARILY HIGH LEVELS OF PHYSICAL CONTAINMENT FOR EXPERIMENTS WITH MANY EUKARYOTIC DNAS.

INTERNATIONAL SHIPMENT AND EXCHANGE OF RECOMBINANT DNA SEQUENCES

THE EMBO COMMITTEE BELIEVES THAT THE PACKAGING AND SHIPMENT OF SAMPLES OF ORGANISMS CONTAINING RECOMBINANT DNA MOLECULES SHOULD BE IN ACCORDANCE WITH ACCEPTED INTERNATIONAL PROCEDURES. IT ALSO BELIEVES THAT IN PRINCIPLE THERE SHOULD BE NO RESTRICTIONS ON THE EXCHANGE OF SAMPLES OF RECOMBINANT DNAS OR ORGAISMS HARBOURING THEM BETWEN SCIENTISTS WORKING IN COUNTRIES THAT HAVE ADOPTED APPROPRIATE GUIDELINES WHICH ENSURE EQUIVAVENT SAFEY PRECAUTIONS. BEFORE A SHIPMENT IS SENT, HOWEVER, THE DONOR SHOULD BE PROVIDED,

BY A RESPONSIBLE OFFICER OF THE RECIPIENT'S INSTITUTION, WITH A WRITMEN STATEMENT THAT THE RECIPIENT HAS THE NECESSARY FACILITIES SPECIFIED BY THE RELEVANT NATIONAL GUIDELINES AND WILL FOLLOW THE SAFETY PRECAUTIONS THEY SPECIFY.

OTHER COMMENTS

DRAFTING AN ENTIRELY SATISFACTORY DEFINITION OF RECOMBINANT DNA MOLECULES IS NOTORIOUSLY DIFFICULT. THE EMBO COMMITTEE WISHES TO MAKE THE FOLLOWING COMMENTS UPON THE DEFINITION PROPOSED BY THE NIH ADVISORY COMMITTEE WHICH READS AS FOLLOWS: 'RECOMBINANT DNA MOLECULES ARE DEFINED AS MOLECULES CONSISTING OF SEGMENTS OF DNA FROM DIFFERENT GENOMES WHICH HAVE BEEN JOINED END-TO-END OUTSIDE OF LIVING CELLS AND HAVE THE CAPACITY TO INFECT SOME HOST CELL AND BE MAINTAINED THEREIN.' IS THE PHRASE 'FROM DIFFERENT GENOMES' TO BE INTERPRETED TO INCLUDE THE GENOMES OF TWO INDIVIDUAL ORGANISMS OF THE SAME SPECIES OR EVEN THE SAME CLONE? THE DEFINITION MAKES NO MENTION OF SYNTHETIC DNA, EITHER CDNA OR CHEMICALLY SYNTHESIZED DNA, AND IT MIGHT BE ARGUED THAT EXPERIMENTS WITH SUCH DNAS ARE EXCLUDED FROM THE GUIDELINES. THE DEFINITION REFERS TO SEGMENTS OF DNA FROM SPECIES 'THAT ARE NOT KNOWN TO EXCHANGE CHROMOSOMAL DNA', THE EMBO COMMITTEE BELIEVES THE WORD 'CHROMOSOMAL' SHOULD BE OMITTED AND SUGGESTS THE FOLLOWING DEFINITION:

' RECOMBINANT DNA MOLECULES ARE DEFINED AS MOLECULES CONSISTING OF SEGMENTS OF NATURAL OR SYNTHETIC DNA WHICH HAVE BEEN COMBINED OUTSIDE LIVING CELLS BUT HAVE THE CAPACITY TO INFECT AND TO BE PROPAGATED IN SOME HOST CELL. NOVEL RECOMBINANT DNA MOLECULES ARE THOSE THAT DIFFER FROM DNA MOLECULES ARISING AT A BIOLOGICALLY SIGNIFICANT LEVEL BY NATURAL PROCESSES.'

SEVERAL NATIONAL GUIDELINES FOR RECOMBINANT DNA RESEARCH STATE THAT CONTAINMENT MEASURES MAY BE RALAXED ONCE A CLONED DNA FRAGMENT HAS BEEN BIOCHEMICALLY CHARACTERIZED AND SHOWN TO BE 'FREE OF HARMFUL GENES' (NIH GUIDELINES) OR 'DEVOID OF ANY KNOWN PATHOGENIC CHARACTERISTIC' (FRENCH GUIDELINES). THE EMBO COMMITTEE BELIEVES THE LATTER TO BE A MORE FEASIBLE REQUIREMENT BUT NEITHER CAN READILY BE MET AND THE COMMITTEE FINDS IT DIFFICULT TO SUGGEST WHAT SORTS OF EXPERIMENTAL TESTS MIGHT BE DEVISED TO MEET THESE REQUIREMENTS. AN ALTERNATIVE MIGHT BE TO REQUIRE THAT NATIONAL COMMITTEES DECIDE UPON REQUESTS TO RELAX THE CONTAINMENT PRECAUTIONS FOR CLONED DNA ON A CASE BY CASE BASIS.

REGARDS, JOHN TOOZE, EMBO, HEIDELBERG

UNIVERSITY OF CALIFORNIA, DAVIS

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COLLEGE OF AGRICULTURAL AND
ENVIRONMENTAL SCIENCES
AGRICULTURAL EXPERIMENT STATION
DEPARTMENT OF PLANT PATHOLOGY

DAVIS, CALIFORNIA 95616

December 5, 1977

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Department of Health, Education and Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Thank you for your letter soliciting comments on the proposed revised Guidelines on Recombinant DNA Research.

We have reviewed the proposed revisions and wish to direct the Advisory Committee's attention to a serious oversight in the Guidelines. After discussing the revisions, particularly the section concerning prokaryotic recombinant DNA, we feel that organisms important in agricultural research were not thoughtfully considered by the Advisory Committee. There exists an ambiguous statement in the proposed revisions that may affect research in the field of agriculture. This statement appears on page 49602 (Federal Register, Tuesday, September 27, 1977), second paragraph, under the section "(2) Prokaryotic DNA recombinants" which reads:

> "Experiments with DNAs from bacteria that are not extensively characterized require P2 physical containment + EK2 host-vector or P3 + EK1. Experiments with DNAs from pathogenic species (Class 2 and plant pathogens, see Appendix B) must use P3 + EK2."

In this sentence, <u>all</u> plant pathogenic prokaryotes are included with CDC (Center for Disease Control) Class 2 animal and human pathogens. We feel that the inclusion of all prokaryotic plant pathogens within this containment category, which seems to imply they are equally as "dangerous" as CDC Class 2 organisms, is an arbitrary assumption made by the Advisory Committee.

As the sentence in the revision now reads, there are no distinctions made among plant pathogenic species, unlike the clear distinctions already assigned to animal and human pathogenic species by an existing CDC classification (Classes 1 through 4 in Appendix B).

We, therefore, wish to submit a classification of plant pathogenic species somewhat analogous to the set-up of the CDC classification. It must be stressed here that the majority of prokaryotic plant pathogenic species are mainly of minimal or no economic importance in agriculture. About 10% that are of economic importance may be so only in areas where a specific crop is cultivated. Otherwise the geographic, climatic and other natural barriers restrict a given host to exist or to be cultivated solely in that area. The same set of conditions restricts the existence of the prokaryotic plant

pathogen, thus the pathogen has to be in close association with the host. Certain plant pathogenic species, of course, should be under stringent containment and restrictions for their containment have been already written into law; that is, organisms of serious agricultural threat are under existing quarantine laws and regulations.

Attached to this letter is a classification based on above considerations in more detail for your consideration and for consideration by the Advisory Committee. The classification provides a realistic view of the status of plant pathogenic species by mainly weighing its economic importance, geographic isolation and cosmopolitan nature. It is difficult to perceive any potential agricultural hazard generated when plant pathogenic prokaryotic genes are clones into E. coli K12, the habitat of which is clearly not on plants.

Sincerely yours,

C. I. Kado

Clarence I. Kado, Professor
Member of the Recombinant DNA Advisory Committee
American Phytopathological Society
Member of the Recombinant DNA Research
Subcommittee, NSF/USDA

N. J. Panopoulos

Nick J. Panopoulos, Associate Professor
Member of the Recombinant DNA Advisory Committee
American Phytopathological Society
Member of the Recombinant DNA Research
Subcommittee, NSF/USDA

Robert J. Shepherd

Robert J. Shepherd, Professor
Member of the Recombinant DNA Advisory Committee
American Phytopathological Society

George Bruening

George Bruening, Professor
Member of the Recombinant DNA Advisory Committee
American Phytopathological Society
Member of the Campus Subcommittee on Recombinant DNA

CIK:rl

Encl.

cc: William J. Garland, Jr.
John W. Littlefield
Peter R. Day
Mary E. Clutter
John Fulkerson
Charles Lewis
Arthur Kelman

PROVISIONAL CLASSIFICATION OF PLANT PATHOGENIC BACTERIA ON THE BASIS OF HAZARD TO PLANTS

Class 1. Minimal or no hazard to plants. (P2 physical containment + EK1 host-vector or P2 + EK2). Of minimal or no economic threat to crops within the state boundaries because the host plant is not present or cultivated in the state; the pathogen is already endemic and found ubiquitously in nature, e.g., in the soil; climatic conditions do not permit survival of the organism and do not favor infection outside the laboratory; or because its host range is limited to a few plants that are not cultivated in the region.

Class 2. Economically important and serious disease causing organisms. (P2 physical containment + EK2 host vector) Host present within state boundaries and is cultivated or grown naturally in large units of land within that state and climatic conditions favor infection in the field. Any species that has known vectors.

Class 3. Plant pathogenic bacteria not present in the United States and under federal quarantine with absolute denial of introduction for whatever reason.

Class 1. Bacterial agents:

Agrobacterium - All listed species: *A. rubi, A. radiobacter, A. tumefaciens, A. rhizogenes*

Corynebacterium - Most plant pathogenic species except as regulated by Class 2 or Class 3 plant pathogens.

Erwinia - All plant pathogenic species except those in Class 2 or Class 3 and when the host, that is commercially propagated is present in the state, e.g., *E. amylovora* is a class II agent in California where the host is grown in large units of land but is Class I in Nevada where the host is not cultivated.

Pseudomonas - All plant pathogenic species except those species restricted as Class 2.

Xanthomonas - All plant pathogenic species except those restricted in Class 2 or Class 3.

Class 2.

All *Corynebacterium* species where their respective hosts exist and where climatic conditions favor the disease. For example, *C. michiganense* in tomato growing regions, *C. sepedonicum* in potato growing regions (Idaho, California).

All *Erwinia* species where their respective hosts exist and where climatic conditions favor the disease. For example, *E. amylovora* in regions cultivating apples and pears (e.g., California, Oregon, Washington, New York, Maine).

All *Pseudomonas* species where their respective hosts exist and where climatic conditions favor the disease. For example, *P. lachrymans* in regions cultivating cucumber (e.g. Wisconsin, Ohio), *P. solanacearum* in tobacco states (e.g., North Carolina, Virginia, Kentucky).

All *Xanthomonas* species where their respective hosts exist and where climatic conditions favor the disease. For example, *X. malvacearum* in regions where cotton is cultivated, (e.g. Texas, Arizona, Mississippi.)

Class 3.

Species that are under quarantine in the United States. Species cannot be brought in from foreign countries. For example, *Xanthomonas citri, X. oryzae, Erwinia vitivora.*

UNITED STATES DEPARTMENT OF AGRICULTURE
AGRICULTURAL RESEARCH SERVICE
PIONEERING RESEARCH LABORATORY
DEPARTMENT OF PLANT PATHOLOGY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN 53706

December 6, 1977

Dr. Donald S. Fredrickson, Director
Department of Health, Education, and Welfare
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

As a research scientist actively working in the field of recombinant DNA, I would like to comment on the proposed revision of the NIH Guidelines as they appear in the Federal Register 42, no. 187, 49596-49609. I wish to specifically address myself to plant pathogens and the manner in which they are handled by the Guidelines. Since plant pathogenic nematodes and fungi are not specifically discussed in the Guidelines, one can include them with the general group labeled lower eukaryotes. However, plant pathogenic bacteria and viruses appear to be special for they are specifically discussed. The following table summarizes my interpretation of the revised NIH Guidelines as they pertain to all plant pathogens. I have placed plant pathogens into one of four groups for direct comparison to the Guideline grouping. The heading, Guideline Group, refers to the outline numbers found in the Federal Register:

Group	Plant Pathogen	Guideline Group	Containment	
1 a	nematodes	III B 1.a.(1)(e)2.	P2+EK1 or P1+EK2	lower eukaryotes
b	"	III B 1.c.	P1+EK1	
2 a	fungi	III B 1.a.(1)(e)2.	P2+EK1 or P1+EK2	
b	"	III B 1.c.	P1+EK1	
3 a	bacteria	III B 1.a.(2)	P3+EK2	
b	"	III B 1.c.	P3+EK1 or P2+EK2	
4 a	virus	III B 1.b.(1)(d)	P3+EK1 or P2+EK2	
b	"	III B 1.c.	P2+EK1 or P1+EK2	

a) refers to shotgun experiments, b) refers to purified DNA experiments

It would appear from the table that plant pathogenic bacteria are by far the most dangerous plant pathogens with virus next and little concern for fungi or nematodes. However, in point of fact, plant pathogenic bacteria and viruses are no more dangerous as plant pathogens than fungi or nematodes and, therefore, should not be arbitrarily placed in a higher containment level. This inconsistency in the Guidelines could be eliminated by changing the containment level of

plant pathogenic bacteria and virus to equal those for fungi and nematodes. Namely, P2+EK1 or P1+EK2 for shotgun experiments.

The second change that should be made pertains to purified DNA experiments (III B 1.c.). Plasmid DNA should not be excluded from those purified DNAs that allow one to reduce the containment level. The Agrobacterium tumefaciens system has clearly demonstrated that plasmid genes alone cannot change E. coli into a plant pathogen. Therefore, if the A. tumefaciens plasmid is adequately purified from chromosomal DNA, there is no danger in cloning parts of it in E. coli at a level of P1+EK1. Further, I believe that the Guidelines should include a mechanism to completely remove cloned DNA combinations from coverage by the Guidelines as data accumulates to show there is no danger.

Finally, I would strongly recommend that a subcommittee be formed to deal with plants and plant pathogens and make specific recommendations for revision of the Guidelines.

Sincerely yours,

John D. Kemp

John D. Kemp, USDA Research Chemist
and Professor of Plant Pathology

jd

cc - Dr. Peter Day, New Haven, Connecticut
Dr. M-D. Chilton, Seattle, Washington
Dr. Gerald Still, Beltsville, Maryland

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO Director, NIH

DATE: December 9, 1977

FROM Director, Office of Recombinant DNA Activities, NIGMS

SUBJECT : Comments of Dr. David Botstein on Proposed Revised Guidelines

On October 31, 1977, Dr. David Botstein of the Massachusetts Institute of Technology briefly addressed the Recombinant DNA Molecule Program Advisory Committee with comments on the proposed revised Guidelines for Research Involving Recombinant DNA Molecules.

Dr. Botstein emphasized that the language in the Guidelines needs to be precise. He was particularly concerned that the proposed revised definition of recombinant DNA is ambiguous with regard to "self-cloning" experiments. He proposed a specific modification in the sentence in the Introduction (Federal Register p. 49596) which deals with the preparation of a list of those combinations of DNAs which are not considered novel. The sentence now reads:

> "The Director of NIH with the advice of the Recombinant DNA Molecule Program Advisory Committee shall prepare the list of those combinations of DNAs (viral, extrachromosomal or chromosomal) which are not considered novel for this purpose and are, therefore, not covered by these Guidelines."

Dr. Botstein proposed that this sentence should be redrafted as follows:

> "The Director of NIH with the advice of the Recombinant DNA Molecule Program Advisory Committee shall prepare the list of those combinations of DNAs (viral, extrachromosomal or chromosomal) which are not considered novel for this purpose and are, therefore, not considered to represent any special hazard simply because they were made in vitro. Ordinary precautions now used in comparable in vivo experiments are sufficient. For example, since Escherichia coli and many other enteric gram-negative species (Salmonella, Shigella, Klebsiella, Serratia, Proteus) recombine in vivo, any and all in vitro crosses among them will not be subject to regulations under these Guidelines."

With regard to the section on Prokaryotic DNA Recombinants (Federal Register p. 49602), Dr. Botstein proposes that the second paragraph be modified as follows (Dr. Botstein's proposed addition is underlined):

> "Experiments with DNAs from bacteria that are not extensively characterized require P2 physical containment + an EK2 host-vector or P3 + EK1. Experiments with DNAs from pathogenic species not known to recombine naturally with E. coli (Class 2 and plant pathogens, see Appendix B) must use P3 + EK2."

Dr. Botstein also strongly felt that the CDC Classification of Etiologic Agents on The Basis of Hazard is out of date.

William J. Gartland, Jr., Ph.D.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director, NIH

DATE: December 9, 1977

FROM : Director
Office of Research Safety

SUBJECT : Exhaust air treatment for P-4 facilities.

Please note on page II-29 of the proposed revised Recombinant DNA Guidelines, it states in paragraph 12 that "the exhaust air from the facility shall be filtered by HEPA filters..." Since there are other methods of fabricating filters which will achieve the required treatment objective, I would like to propose that we add the phrase "or equal" after "HEPA filters." This will allow those institutions that have in the past fabricated their own filters to meet the intent of these Guidelines; for example, the Microbiological Research Estate at Porton, England have over the years constructed their own filters out of fiberglass mat material. These filters are then tested against the same efficiency standards employed in the certification of "HEPA filters." Also the exhaust air treatment at the Fort Detrick facilities have relied on on-site fabrication of fiberglass filters. This proposed change does not alter the intent of paragraph 12. It does, however, recognize commonly accepted approaches used in the treatment of exhaust air from maximum security containment facilities.

W. Emmett Barkley /ef
W. Emmett Barkley, Ph.D.

km

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director, NIH

DATE: December 9, 1977

FROM : Chief, Laboratory of Viral Diseases, NIAID

SUBJECT : Recommended change in revisions of the guidelines

On page IV-5 the statement "Individuals receiving antibiotics should not work with prokaryotic host-vector systems during therapy nor for seven days thereafter." needs revision. The primary purpose of the requirement is to avoid work with E. coli host systems while the person is undergoing changes in bowel flora that might facilitate colonization. As written, the sentence does not include sulfonamides, and does not exclude chronic antimicrobial regimens to which the bowel flora would be equilibrated. I propose the following substitution "Individuals receiving antimicrobial therapy expected to affect the bacterial flora of the gastrointestinal tract should not do recombinant DNA research involving prokaryotic host-vector systems during therapy nor for seven days thereafter. Examples where this restriction would not apply are persons on prolonged antimicrobial suppression such as for rheumatic fever prophylaxis or suppression of urinary tract infection."

Wallace P. Rowe, M.D.

sg

NATIONAL SCIENCE FOUNDATION
WASHINGTON, D.C. 20550

OFFICE OF THE
DIRECTOR

December 9, 1977

Dr. Donald S. Frederickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

As you know, in August 1976 the National Science Board adopted substantial parts of the guidelines of the National Institutes of Health (NIH) on the conduct of recombinant DNA research as National Science Foundation policy. I am now pleased to advise you that at its meeting on November 17, 1977, the Board adopted a resolution, of which a copy is enclosed, endorsing both the process by which the NIH has been revising the guidelines and the efforts of the NIH to publicize the proposed revisions.

The Foundation is particularly pleased with the continuing efforts to keep the guidelines flexible and adapted to new scientific developments. We remain anxious to cooperate with you in your efforts to ensure both the safety of the public and the advance of science to the public benefit.

Sincerely yours,

Dick

Richard C. Atkinson
Director

Enclosure

cc: Dr. Norman Hackerman, Chairman, NSB
Dr. Eloise Clark, Assistant Director for Biological, Behavioral, and Social Sciences, NSF

RESOLUTION ADOPTED BY THE NATIONAL SCIENCE BOARD AT ITS ONE-HUNDRED AND NINETY-FOURTH MEETING ON NOVEMBER 17-18, 1977

The National Science Board unanimously requested that the Director of the National Science Foundation convey to the Director of the National Institutes of Health its endorsement of the process used to update the guidelines for the conduct of recombinant DNA research. The original guidelines were developed on the basis of scientific information available approximately two years ago. The proposed revisions have been developed on the basis of new information accumulated during the intervening period, in particular, those concerning the biology of organisms containing recombinant DNA molecules and the effectiveness of biological and physical containment. Reassessment will undoubtedly be needed again in the future as new knowledge becomes available, as cited in the earlier resolution of the Board.

The Board also endorsed the activity carried out by the National Institutes of Health in widely publicizing the proposed revisions in such a way as to ensure full participation of scientific, industrial, agricultural, environmental, and other concerned public groups in the process.

The National Science Board looks forward to continuing cooperation with the National Institutes of Health in this area of mutual concern.

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COLLEGE OF NATURAL RESOURCES
AGRICULTURAL EXPERIMENT STATION
DEPARTMENT OF PLANT PATHOLOGY

BERKELEY, CALIFORNIA 94720

December 9, 1977

Dr. D.S. Fredrickson, Director
National Institutes of Health,
Department of Health, Education and Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Thank you for your letter and the copy of the draft version of the proposed revisions of NIH Guidelines for Recombinant DNA Research. Having reviewed the proposed revisions I would like to offer the following comments for consideration by you and by the Recombinant DNA Molecule Program Advisory Committee at its next meeting:

At the risk of being somewhat repetitious, but in order to retain clarity and perspective in my comments, I would like to state from the outset what I perceive to be the essential but separable potential biohazard components of in vitro DNA manipulations and some of the basic purposes of the NIH Guidelines:

Two basic biohazard components can be distinguished: primary and secondary. The first include (a) the potential for converting the cloning host (primary host) into a pathogen or into an otherwise undesirable organism, and (b) the potential of such primary host to escape and become established into a congenial or uncongenial habitat. The secondary biohazard components are: (c) the "runaway" of recombinant molecules into hosts other than the one used for cloning (secondary hosts), and (d) the potential for such organisms to perform as in (a) and (b).

The Guidelines presumably aim at (i) prohibiting experiments such as those

aiming directly at the construction of highly virulent primary hosts (e.g. the botulinum toxin experiment) or other operations of high potential risk, and (ii) assigning containment levels for all permissible experiments in such a manner that the probability of events a, b, c, or d above are lowered to an acceptable, reasonably safe level.

The following paragraphs contain comments pertaining to general as well as specific aspects of the proposed revisions. Some of these comments pertain specifically to experiments with plant pathogenic bacteria, in which I have an active interest, and with which special problems have existed and new ones have arisen in view of the proposed revisions.

1) Redefinition of recombinant DNA molecules. The proposed new definition is a meaningful one, indeed, and should be retained.

2) Proposal to regulate only those experiments involving "novel" recombinant molecules. This is also a welcome change. It recognizes a basic conceptual dichotomy which existed in the original guidelines: the intent to regulate strictly one way of constructing a particular bacterial strain (in vitro) but not another (in vivo). Unfortunately, elements of this dichotomy have persisted in the proposed revisions (see under 3 below).

Given the present state of affairs, in which neither the Committee nor the currently pending bills in Congress propose to regulate in vivo genetic manipulations, it is quite obvious to me that many kinds of in vitro cloning experiments which involve procaryotic DNA and host-vectors, (e.g. the cloning of a particular type of DNA in a host in which the DNA is normally present, or by which it can be acquired naturally) involve biohazards of a similar nature and magnitude to those inherent in many "standard" in vivo manipulations. Accordingly, I quite agree with the basic idea of distinguishing between experiments involving "novel" and "non-novel" molecules.

However, I think that the wording of the proposed definition of "novel" DNA molecules could be further improved and simplified. For example, "novel" molecules can be defined more simply as "molecules consisting of segments of DNA derived from genomes that are not known to replicate within the organism used to propagate the recombinant DNA molecule." The situation where two species are known to exchange chromosomal DNA is a partial case of this. It should be further remembered that two different species which exchange chromosomal DNA could contain plasmids or phages that are species-restricted and do not integrate with the chromosome of the host species. Accordingly, the cloning of DNA from such elements in a chromosome-exchanging host cannot be strictly considered as "non novel".

Having argued in favor of maintaining the proposal to deregulate experiments not involving "novel" recombinant molecules I wish to point out certain corollaries which result directly from this concept and which must, in my opinion, be appropriately taken into consideration if the Guidelines are to be internally consistent:

3) Conjugative mobilization of recombinant plasmids from the primary cloning host. I would like to propose that the committee consider the possibility of allowing the use of conjugative plasmids to mobilize procaryotic recombinant molecules, for example, from HV-1 procaryotic systems. This experiment is now prohibited de facto, since HV systems in general are required to be free of conjugative plasmids. My reasons are explained in the following paragraphs.

Let's assume that an investigator is interested in identifying and/or isolating segments of DNA, from a particular source bacterium A, which complement a particular phenotype in certain mutants of that organism.

Theoretically, the investigator has the following options:

Option(i): If bacterium A is transformable and a vector capable of replicating in it is available, the investigator could clone DNA from A directly into the mutants. Alternatively, the investigator could construct a "colony bank" by cloning the DNA from bacterium A using A as the host. He would then reintroduce recombinant molecules into each mutant of A, either by transformation with DNA extracted from the recombinant clones, or by conjugative mobilization using an appropriate conjugative plasmid as a mobilizer. Such a plasmid, if not already present naturally, can be introduced artificially into the cloning host prior to the initial cloning step or subsequently, into the individual recombinant colonies, for example, by performing triparental crosses.

None of the above steps would involve "novel" recombinant molecules; therefore, none of the regulations contained in the proposed revisions will apply. Thus, (1) organisms A and the vector plasmid will not have to be certified as a host-vector system; (2) A could contain conjugative plasmids; (3) the construction of strains simultaneously carrying conjugative elements and "non-novel" recombinant plasmids would not be prohibited (4) in fact, the vector plasmid could be a conjugative one (for example, RP4 or RK2!). According to the revisions, the investigator could also transfer his recombinant plasmids to any organism with which organism A can exchange chromosomal DNA by natural physiological processes and in which the plasmid vector could normally replicate, without having to comply with regulations.

Option (ii): The investigator could construct a "colony bank" using DNA from bacterium A and another bacterial host B, with which A may not exchange chromosomal DNA by natural physiological processes but which satisfied better the technical prerequisites of transformability, vector replication, recombination-

deficient background, etc., for example, E. coli. This experiment would be subject to regulation. Therefore, in attempting to introduce the recombinant molecules from the "colony bank" B into the various mutants of the source organism A., the investigator is de facto (and absolutely) restricted to transformation since the current guidelines, as well as the proposed revisions, effectively prohibit conjugative mobilization by not allowing for the simultaneous presence of conjugative and "novel" recombinant plasmids in the same host. The paradox is obvious: it is apparently all right to clone DNA from organism A using A itself, or another organism with which A exchanges chromosomal DNA, as the host, even though these may contain conjugative plasmids (free or integrated), or using a conjugative plasmid as a vector, and to transfer or mobilize such recombinant molecules from these hosts to organisms X, Y, or Z with which A exchanges chromosomal DNA, since no "novel" recombinant molecules (as defined in the proposed revision) are involved in any of the steps mentioned; it is not all right, however, to perform the conjugative mobilization of the same molecules from another cloning host B, which does not exchange chromosomal DNA with A, under any circumstances!

The P + HV containment levels assigned under the Guidelines are presumably commensurate with the probability that host B may be converted into a pathogen. Therefore, it is the secondary biohazards of option (i) and (ii) above that must be compared. I know of no general rules that suggest that the intrinsic escape potential of recombinant plasmids from various unmodified (HV-1) procaryotic (Gram negative) primary cloning hosts, such as organisms A and B above, is not likely to be comparable. Granted, the likelihood of secondary transmissions from such systems will be habitat-dependent. But in the absence of experimental data, habitat-dependent secondary transmission from

such hosts can only be judged in very hypothetical and general terms.

The hypothetical bacterium A which I have used in my analysis could well be, for example, Rhizobium sp. or Agrobacterium tumefaciens, both of which are transformable, although not as efficiently and reproducibly as E. coli.

I would like, therefore, to suggest that a provision is made in the Guidelines to allow for the circumstances under which conjugative plasmids may be introduced into HV-1 procaryotic hosts carrying "novel" recombinant molecules of procaryotic origin to perform, for example, triparental crosses, but to require that the physical containment level for such experiments be raised one step. Perhaps experiments involving DNA from certain classes of pathogenic organisms could be excluded from such a provisions.

I feel that such a provision can be justified on several grounds: (i) one could use additional safeguards to avoid co-transfer of the mobilizing plasmid to the recipient which receives the recombinant plasmid (e.g. suppressor-dependent or temperature-sensitive Tra^- mutants, or plasmids which establish mating pairs but do not stably replicate in the recipient host); and (ii) although rarely pointed out in discussions of biohazards, the effective prohibition of, or undue restriction on, in vitro genetic experiments will have adverse effects from the standpoint of biosafety in genetic experiments with bacteria in general: by effectively preventing the use of the cloning method through regulations such as those I have just described, researchers will naturally resort to classical in vivo methods such as conjugational crosses in their work. Needless to say that such experiments, although not covered by the Guidelines and presumably occur naturally, are not biohazard free. Many researchers, including those of us working with plant pathogenic

bacteria, use the wide-host range P plasmids as conjugative vehicles in a variety of bacteria. These plasmids transfer to almost any Gram negative species with bacterial chromosomes and other plasmid replicons. Derivatives(P') of these plasmids carrying segments of chromosomal material from such diverse organisms as E. coli and P. aeruginosa have been obtained. Recently, P-plasmid-Mu phage cointegrates have been used to induce the transposition of bacterial chromosomal segments onto the plasmid. Apparently this method works in species other than E. coli as well. Secondary transfers of such P' elements could be judged as even more biohazardous than, for example, "run-away" ColE1- or PSC101-recombinant plasmids, the vectors of which have a much more restricted host range than the P plasmids. Furthermore, co-transmission of non-clustered genes is much more likely to occur by conjugation, which allows for the transfer of extended regions of "donor" DNA, than by individual in vitro recombinant plasmids, each of which is likely to carry only a short segment of "donor" DNA, and more than one of which would not normally be co-acquired by or co-maintained in the same host cell because of incompatibility. The proposal which I have put forward will likely bring more genetic experiments under the regulatory umbrella and presumably increase the overall biosafety in bacterial genetic work.

4) The status of experiments involving "non-novel" recombinant molecules and HV systems of organisms under blanket prohibitions. The status of prohibition (i) relating to experiments involving the cloning of DNA derived from the pathogenic organisms in CDC classes 3, 4, and 5, moderate risk oncogenic viruses or cells infected with such agents, should be clarified. Under the Guidelines, such experiments are prohibited regardless of the host-vector system used. But since the Guidelines will not apply to experiments not involving "novel" molecules the cloning of such DNAs in the host or origin

would be judged to be permissible. If the intent is to de-regulate such experiments, prohibition (i) is inconsistent. If, on the other hand, the intent is to prohibit such experiments, even when "novel" DNAs are not involved, the proposed deregulation paragraph should indicate specifically that deregulation does not apply to prohibition (i).

Similar arguments could be presented with regard to prohibition (ii).

5) Prohibition III. (a) In the original guidelines "The deliberate creation from plant pathogens of recombinant DNAs that might increase virulence and host range" was totally prohibited. In the revised Guidelines, this prohibition applies to "The deliberate creation by use of recombinant DNA of plant pathogens with increased virulence and host range beyond that which occurs by natural genetic exchange." This revision is a meaningful one. However, while I do not disagree with the spirit of prohibition III, I find it not entirely fair since it applies only to plant pathogens. Similar experiments are not totally prohibited with CDC class I or II organisms.

To circumvent this problem two possible revisions can be suggested: (i) omit the word "plant" so that prohibition III applies equally to all pathogens not covered by prohibition; (ii) propose a classification of plant pathogens according to risk similar to the CDC classification (no such classification exists presently). Prohibition III could then be maintained as such for high-risk phytopathogens, but could be lifted for those which are judged to be of low risk. I personally favor the latter approach.

(b) Another point concerning prohibition III should be made also. Increases in virulence or host range may occur naturally by mutation, in addition to gene exchange. Strictly interpreted the revised prohibition III would require that the origin of a plant pathogenic strain different in varietal specificity should be traced to natural exchange. Strains which have acquired

the ability to infect a particular host variety which is normally resistant do occur in some plant pathogens. I seems desirable, therefore, to add the words "or mutation" at the end of prohibition III.

(c) In view of the newly proposed concept of "novel recombinant DNAs" vs. "recombinant DNA" sensu stricto, I wonder whether or not the word "novel" should be added between "use of" and "recombinant DNA" in prohibition (iii) to improve clarity.

6) Re-classification of experiments involving ("novel") recombinant DNAs from procaryotic plant pathogens in E. coli K12 hosts. The original Guidelines recommended the use of P2 + EK1 or P2 + EK2 levels of physical and biological containment for the construction of recombinant DNAs from procaryotic plant pathogens which normally exchange DNA with E. coli. Type of DNA exchanged was left unspecified. Those that do not, required P3 + EK2 level. No distinction between "novel" and "non-novel" recombinant molecules was made. These levels were similar to the levels proposed for the cloning of DNA from procaryotic human pathogens included in Class 2 of the CDC classification (e.g. Salmonella, Shigella). DNA's from plant pathogenic fungi and viruses could be cloned in E. coli under P3 + EK2 and P3 + EK1 on P2 + EK2 respectively. In the current revisions the containment requirements for "novel" DNA's from procaryotic pathogens (plant plus human pathogens of CDC class 2 that are not known to exchange chromosomal DNA by with E. coli) have been increased to P3 + EK2 levels!

The reasons for this increase (1 or 2 steps) are not clear to me and I must express my deep surprise, particularly in view of the following comparisons of proposed containment levels for other plant pathogens: (i) experiments involving DNA from lower eucaryotes that produce potent non-polypeptide toxins that affect plants (e.g. several plant pathogenic fungi) were lowered by

one step (from P3 + EK2 to P2 + EK2 or P3 + EK1). (ii) Containment levels for plant virus DNAs in EK hosts were not changed (P3 + EK1 or P2 + EK2). (iii) In both cases the levels are lower by one step compared to the P3 + EK2 level required for plant pathogenic procaryotes. These, although not known at present to exchange chromosomal DNA with E. coli, do exchange plasmid and/or viral DNAs, whereas no natural genetic exchange of any kind has been shown or is likely to occur between fungi or plant viruses with E. coli.

Since I basically agree with the approach which has been followed in dealing with lower eucaryotes, I suggest that a similar approach be used, when applicable, for procaryotes as well. Furthermore, containment levels for experiments with procaryotic DNA in EK hosts should remain one step lower than those for various types of lower eucaryotic or viral plant pathogic DNAs involving a similar potential biohazard, since the former are much more likely to be introduced into these hosts than the latter by standard in vivo manipulations.

I wish to make a final general comment: if the Guidelines are to survive, they should take into account, among other things, (i) the comparative risks of in vivo (or "natural") and in vitro ("novel") methods of accomplishing a particular experimental goal (e.g. the construction of a particular strain), and (ii) the possible indirect consdquences of over-regulating one experimental method (in vitro) over another (in vivo) which, although "natural", is not necessarily all that biohazard-free. It is clear that the basic revisions proposed are meaningful and overdue and that the original stringency has already caused much unnecessary delay in certain areas of research. Stringency and overregulation, however appealing to some, can indeed have undesirable side-effects, since classical genetic research is not entirely

risk-free.

I do appreciate the opportunity to express my views.

Sincerely,

N.J. Panopoulos

N.J. Panopoulos
Assistant Plant Pathologist and
Lecturer

JAMES R. SANDERSON
533 LAKESIDE DRIVE, S. E.
GRAND RAPIDS, MICHIGAN 49506

10 December 1977

Mr. Donald Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Mr. Fredrickson:

Upon returning from a trip recently I found in my mail a note from Scientists' Institute for Public Information saying that proposed revisions of the Guidelines on Recombinant DNA Research published by NIH have been published for comment, and that comments will be presented to the Advisory Committee on December 15th. SIPI suggested that if interested I obtain a copy of the proposed revisions and submit my comment. I have not had time to see the proposed revisions but can let you know how I feel about recombinant DNA research.

I am strongly opposed to any and all recombinant DNA research.

To say that a scientific research should be pursued because an enabling technique has been discovered is not a valid reason, especially when no one can foretell whither it may lead for good or ill.

The fact that scientists of great prominance favor this research and are even engaging in it or planning to means to me that they are irresponsible or that they are men whose scientific knowledge is of narrow breadth and insufficient depth. This is not the first instance of such a situation.

I would remind you that there are also scientists of equal standing who oppose this research.

I have been in "super-safe" laboratories and understand the methods and procedures of their design and use. I know that humans working in them become casual about the procedures. As to whether the requirements in the NIH guidelines are adequate to eliminate all possibilities for irreversible, subtle, and desperately harmful results I am skeptical. What is our assurance that they will be followed? Who will police them? Furthermore, I understand they only apply to laboratories engaged on government contracts.

I think I have read that some chemical or pharmaceutical concern has applied for a patent on a product of recombinant research. This suggests many questions. If true, I suppose the only control is the conscience of the maker, and what motivations have guided that?

Speaking of motivations, let me quote from the Atlantic Monthly of last February: (There had been long discussion at the University of Michigan as to whether they would build a supersafe lab and undertake this research)-

> "Several of the faculty had come to believe that gene transplantation, like the military research disputed a few years before, was work that a univsity simply should not do." A professor brought the discussion to a head by tese remarks: "During the past fifteen to twenty years, we have let slip through our fingers numerous opportunities to establish a strong cell-and-molecular-biology program here. At the moment, the university has a favorable position with respect to research on recombinant DNA. It is perfectly clear that other universities will proceed with ...resaerch on this subject. Should Michigan chose not to, we will lose our position; this interested faculty will, of course, go elsewhere; our recruitment in this and related areas will falter; and we will suffer a blow to our excellence."

'Nuff said: the university has built the lab, and just recently the papers say the research has begun.

Since you know nothing of me, - I'm a conservative, just too young to have voted for Taft, but did for Hughes. Yale graduate. Have held top secret clearance fro both the AEC and the Pentagon. I'm the second man in this quote from Jacques Barzun: "It is an error to suppose that when a physicist talks about science he is more reliable than a so-called layman who has taken to inform himself and to think."

With assurances of my esteem, Iam,

Sincerely yours,

J R Fredrickson

cc: SIPI

NATIONAL RESEARCH COUNCIL
ASSEMBLY OF LIFE SCIENCES
2101 Constitution Avenue Washington, D. C. 20418
DIVISION OF MEDICAL SCIENCES

December 13, 1977

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Building 1, Room 124
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Dr. Philip Handler, President of the National Academy of Sciences, has requested that the attached statement of the Committee on Laboratory-Created Biohazards of the National Research Council be forwarded to you. The statement is in response to your request for comments on the "Revised Guidelines for Recombinant DNA Research."

The Committee is composed of Maclyn McCarty, Chairman, Paul Berg, Clifford Grobstein, Cyrus Leventhal, Charles Rammelkamp, Arthur Kelman, Charlotte Friend, Herman Eisen, and Rollin Hotchkiss.

I trust that the statement will be of use to you in your deliberations.

Sincerely yours,

Daniel L. Weiss

Daniel L. Weiss, M.D.
Executive Secretary

DLW:jdn

Attachment

cc: Dr. McCarty

The National Research Council is the principal operating agency of the National Academy of Sciences and the National Academy of Engineering to serve government and other organizations

Statement of

THE COMMITTEE ON LABORATORY-CREATED BIOHAZARDS

We have considered the pending "Revised NIH Guidelines for Recombinant DNA Research" (DHEW Publication (NIH) 77-99, Summer 1977). We have every reason to believe that the Recombinant DNA Molecule Program Advisory Committee has functioned conscientiously and effectively and that the general thrust of the recommendations is appropriate. We will not attempt to either add to or subtract from the cogency of their specific recommendations.

We have, however, certain comments which we believe deserve consideration with respect to the Guidelines as they have operated and will continue to operate after this revision cycle. We put these comments in the form of suggestions for the Advisory Committee and for the Director of the National Institutes of Health and his staff as they seek to implement and adjust the Guidelines to fit advancing knowledge.

1. Time of Revision Action: We are concerned by the long delay between the time the revisions are proposed by the Advisory Committee and the time they are approved by the Director of the NIH. There have also been long delays in the certification of approved host-vector systems. While we are aware of the requirements for ample review and comment, we suggest that careful review of the process may eliminate unnecessary delays. Several other suggestions noted below may contribute to the improvement of this process, but we particularly urge that the process be reviewed as a whole for the purpose of reducing the time required for a revisory action (perhaps 90 days).

2. Institutional Biohazards Committees: A key to the success of the self-regulatory concept of the Guidelines is the effective operation of the Institutional Biohazards Committees. We urge that a study of the operations of these committees be instituted as soon as possible. Particular attention should be given to the standards established by the committees for institutional approval of research, the composition of the committees, the breadth of jurisdiction of the committees within their respective institutions and their "clout" in administrative terms, and the costs and funding of the operation of the committees. Consideration should also be given to mechanisms for sharing experiences among the several committees and to special grants to cover their expenses. Too often such costs must compete at a disadvantage for restricted local administrative budgets.

3. Continuing Reassessment and Revision: The consensus of our Committee is that a continuing reassessment and revision of the Guidelines could be expedited and made more comprehensive by the establishment of ad hoc panels of experts charged with periodic examination and review of specific scientific issues related to recombinant DNA research, as well as to problems of the administration and implementation of the Guidelines. The panels would report to the Advisory Committee for a second-level review prior to submission to the Director of the NIH.

Several areas particularly worthy of such efforts are:

a. Cloning of and with Eucaryotic Virus Genomic Segments: The containment requirements for experiments involving cloning of eukaryotic, particularly mammalian, DNA and RNA viral genomic segments in prokaryotic host-vector systems and the use of presently available animal virus DNA vectors for cloning or integrating pro- and eukaryotic DNA segments in their respective animal cell hosts.

b. Cloning of Synthetic DNA Sequences: The containment recommendations for propagating synthetic DNA sequences in pro- and eukaryotic host-vector systems, and particularly those for production of the products coded by these synthetic segments.

c. Plant Recombinant DNA Studies: The containment requirements for cloning experiments that involve (i) DNA from plants, their viruses and other pathogens in vectors capable of propagating in plant cells and (ii) the use of plants or plant cells modified by recombinant DNA methods.

We considered this proposed panel to be of unique importance, and therefore offer the following extended commentary on plant recombinant DNA studies:

The primary emphasis of the Guidelines is appropriately directed towards minimizing any possible hazards to man that might arise from research using recombinant DNA techniques. The potential benefits of such research to the agricultural sciences and the magnitude of future efforts required to exploit these benefits suggest the need for improved mechanisms whereby viewpoints in this area can be brought to the attention of the Advisory Committee. This can be done by establishing one or more panels to consider in depth the full application of recombinant DNA technology to the advacement of knowledge in plant breeding and genetics, plant nutrition (including nitrogen fixation), plant physiology and biochemistry, and plant pathology. It may be advisable to constitute a separate panel to give special consideration to invertebrate virology, animal and veterinary science, and entomology. The USDA-NSF-sponsored meeting at Airlie House in April 1977 provided an opportunity for plant and animal scientists to consider how regulation of recombinant DNA research might affect research in agriculture and other non-medical areas. A number of important subjects were raised at this meeting, and recommendations were forwarded to the Advisory Committee. Advice in these areas should be transmitted on a regular basis from expert panels in these scientific fields. Agricultural and non-medical interests can best be served by the development of advisory panels representative of these fields, which can transmit their findings and recommendations to the Advisory Committee for synthesis into the continuing revisions of the Guidelines.

4. Responsibilities for Compliance: The Guidelines specify that Principal Investigators have the primary responsibility for implementing

the Guidelines. The institutional Biohazards Committees and the Biological Safety Officers shall assure, among other things, that the laboratory safety procedures are rigorously followed. There is an implication that the staff of the NIH has a responsibility to ensure that all NIH-funded research conform to the Guidelines. It is indicated that a major factor contributing to the expectation that the Guidelines will be followed is "the fact that non-compliance will result in termination of funding." Other factors, such as peer pressure and publication review, will contribute to the general expectation that there will be compliance.

There are many specific questions concerning the procedures which will be followed by the staff and Director of the NIH in carrying out their responsibilities. This is particularly true with respect to possible NIH monitoring of compliance and/or termination of funding. The general public and the scientific community should know in advance (a) who could bring charges of non-compliance, (b) how charges of non-compliance would be evaluated, (c) what opportunities the Principal Investigator and his institution would have to defend themselves against such charges, and (d) what procedures would be followed before termination of funding or other penalties are invoked.

5. Risk-Assessment Studies: We are generally concerned with the problem of conducting risk-assessment studies under the present strictures stated in the Guidelines. For example, how can experiments devised to increase our knowledge of risk be undertaken when such experiments are specifically forbidden under the Guidelines and may even be subject to legal strictures? We suggest that the Director of the NIH consider plans whereby risk-assessment experiments can be appropriately designed and carried out, and to consider the specific characteristics of control and containment under which such information can be safely obtained.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
77 MASSACHUSETTS AVENUE
CAMBRIDGE, MASSACHUSETTS 02139

DEPARTMENT OF BIOLOGY
Room 56-721
PHONE: (617) 253-1000

December 14, 1977

Dr. Donald S. Fredrickson
Director
Bldg. 1, Room 124
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

We submit herewith a request from a group of scientists working on various aspects of the biology of Salmonella typhimurium for a clarification of the status of laboratory strains of this organism as hosts for recombinant DNA involving Salmonella DNA and, in some cases, E. coli K12 DNA. As you know, your advisory committee suggested that such experiments should be permitted under the current NIH guidelines. However, permission to proceed has not been forthcoming from your office. The appended letter has been approved for signature by eleven concerned scientists wishing to see this permission granted; they represent much of the Salmonella community active in molecular genetics today.

In the letter, we have limited ourselves to the scientific issues: the benefits to research as we see them and our best estimate of the magnitude of the risk that might be imagined. In this covering letter, the undersigned wish to point out a few, more political, considerations. These are as follows:

1. The guidelines as written do not explicitly forbid the experiments proposed. In the Federal Register (p. 27918) the relevant passage of the NIH Guidelines is as follows: "In general, the strain of any prokaryotic species used as the host is to conform to the definition of Class I etiologic agents given in ref. 5 (i.e. Agents of no or minimal hazard.***) and the plasmid and phage vector should not make the host more hazardous." (our emphasis). We submit that this language explicitly envisions that particular strains of species formally in other classes are permissible within the Guidelines provided that the particular strain presents "no or minimal hazard". Further, we cannot see why the phrase "In general" would be included were it intended to have absolute ban on non-Class I agents. In the appended letter we try to document the idea that strain LT2 of Salmonella typhimurium is not an appreciable hazard and thus conforms to the definition of Class I.

2. All the recombinants anyone here proposes to insert into strain LT2 could be made *in vivo*. The only difference is the labor (which could be immense) involved in finding the right ones. The *in vitro* methods make certain experiments (such as sequencing the Ames tester mutations) practically feasible.

3. Failure to permit reasonable and non-hazardous experiments which are within the spirit and the letter of the Guidelines is demoralizing in the extreme to a productive community of scientists whose contributions include some of the most useful techniques and results of molecular genetics. We do not believe that the current predicament is the result of reasoned intention to prevent absolutely *Salmonella* experiments; we think that the situation is the result of a simple oversight since the Advisory Committee could not think of every possibility. Since the guidelines are supposed to regulate, but not to forbid reasonable work, we cannot understand why our field should be singled out for an absolute prohibition; after all no one has actually suggested *Salmonella* to *Salmonella* recombinants constitute a hazard.

In conclusion, we hope that you can consider our position and that you will allow us to proceed, under the same rules that apply to everyone else, with our experiments.

Sincerely yours,

David Botstein
Associate Professor of Genetics
Massachusetts Institute of Technology

John Roth
Professor of Biology
University of Utah

Enclosures

December 14, 1977

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

At the suggestion of Dr. Perpich, we are writing to you to try to clarify the issues surrounding the problem of *in vitro* recombination experiments in laboratory strains of *Salmonella typhimurium*. It seems to us that there are two points of importance: First, that there is a body of scientific knowledge of great and general interest which can be gained from such experiments in *Salmonella* which cannot be obtained as easily or at all using *E. coli* K12. Second, that the laboratory strains of *Salmonella typhimurium* in question (all derivatives of strain LT2) if handled with normal precautions do not pose any significant risk of causing infections in man.

With respect to the first point, we wish to only briefly state that there are interesting phenomena and practical applications of molecular biology which depend upon *Salmonella*. Mutagenesis tests for potential carcinogens developed in the Ames laboratory use tester mutants whose nucleotide sequence would be of great interest. Application of current technology to this sequencing is made extremely difficult by the current interpretations of the NIH Guidelines (1-4). The exciting progress in the understanding of phase variation (thus far only clearly described in *Salmonella*) is one of the first really new results to arise because of recombinant DNA methods (5). In that case *Salmonella* DNA was put into *E. coli*. Further genetic analysis of this mechanism awaits, in great measure, permission to return these DNA molecules to their original organism. A more detailed presentation of the virtues of *Salmonella* research is appended. Next to *E. coli*, *Salmonella* is genetically the best understood free living organism on earth (6,7).

In respect to pathogenicity of laboratory strains, we offer the following. Strain LT2 and its immediate derivatives are the only strains we wish to consider for *in vitro* recombinant DNA work. Virtually all *Salmonella* genetics has been done in these strains. Informally, we have polled many of the major laboratories using this organism. Under standard conditions of use, we know of only six possible laboratory infections among more than 1000 persons-years. Of these, one is published as having been caused by strain LT2 (8), but the strain in question is, in fact, a derivative of the more virulent strain LT7 (9); another turns out also not to be LT2 but a strain which came from a hospital isolate relatively recently and which differs antigenically from LT2. All of the remaining cases were caused by improper laboratory practice (i.e., resuspension of concentrated pellets by mouth pipetting) and followed an oral dose of more than 10^9 organisms.

The low incidence of laboratory infections with LT2 is to be contrasted to the case of natural isolates of Salmonella which can cause gastrointestinal disease with inocula of as few as 1000 organisms. Consistant with this view are experimental data on mice obtained in the Stocker and the Botstein laboratories; in both cases particular laboratory LT2 strains were tested directly and found to be 1,000 times less virulent than Salmonella typhimurium strains isolated independently from nature. An additional important point is that LT2 infections, when they occur, appear to be self-limiting. We know of no case of secondary infection by LT2. Our point is that, based on danger of laboratory infection, strain LT2 stands in relation to natural isolates of Salmonella typhimurium much as E. coli K12 stands to natural isolates of E. coli, some of which cause serious disease.

The final point which we would like to bring to your attention is that the NIH Guidelines incorporated, as a convenience, the CDC classification of bacteria according to pathogenicity. We do not believe that this convenience should cause NIH to prevent (absolutely in the present case) experiments with particular strains clearly less virulent than many CDC "class I" organisms. We do not believe that the scientists who framed the Guidelines and who made use of this convenience intended to prevent the use of Salmonella typhimurium LT2 or other strains of formal pathogens whose virulence has been shown by experience and experiment to be of low virulence.

We do not know of any scenario by which introduction of LT2 DNA back into LT2 increases the virulence of LT2 since no new DNA combinations are being created. Even transfer of E. coli DNA into Salmonella generates no DNA combinations which could not occur in nature and which cannot now be made by genetic means. Both plasmid and chromosomal DNA pass easily between Salmonella and E. coli (10,11,12). Many Salmonella diploids and interstrain hybrids between Salmonellae (including highly virulent strains) have been made over the past fifteen years with no ill effects.

What we would like you to do is to concur with your advisory committee and permit the introduction of in vitro recombinant DNA from Salmonella and/or E. coli into Salmonella typhimurium LT2 and its derivatives. Thus, we request permission to use in vitro cloning techniques to construct strains which can already be made by strictly genetic means. Use of new technology merely makes the task orders of magnitude easier. If permission to transfer cloned Salmonella DNA to Salmonella is granted, we are in a position to promise that interesting science will result (see Appendix), and that this involves no risks beyond those encountered in current laboratory work. These risks can be easily managed by good laboratory practice.

The eleven signers are all actively engaged in Salmonella genetics. They are:

Bruce Ames
Department of Biochemistry
Univ. of Cal., Berkeley

Giovanna F. Ames
Department of Biochemistry
Univ. of Cal., Berkeley

David Botstein
Department of Biology
Mass. Institute of Technology

John Ingraham
Department of Microbiology
Univ. of Cal., Davis

Nancy Kleckner
Dept. of Biochemistry and Molecular Biology
Harvard University

Daniel E. Koshland
Department of Biochemistry
Univ. of Cal., Berkeley

Boris Magasanik
Department of Biology
Mass. Institutes of Technology

John Roth
Department of Biology
University of Utah

Melvin Simon
Department of Biology
Univ. of Cal., San Diego

Bruce A.D. Stocker
Department of Medical Microbiology
Stanford University

Graham Walker
Department of Biology
Mass. Institute of Technology

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Dr. Fredrickson

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THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE

DEPARTMENT OF MICROBIOLOGY

725 N. WOLFE STREET
BALTIMORE, MARYLAND 21205

December 16, 1977

Dr. Donald S. Fredrickson
Director, National Institutes of Health
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Bernard Talbot asked me to submit a suggested definition of recombinant DNA that would include synthetic genes. I suggest addition of a footnote to the definition given in the Introduction of the draft of revised guidelines dated 6/23/77, as follows:

"Synthetic genes, i.e., polydeoxynucleotides coding for natural polypeptides (or analogs thereof) that are synthesized chemically or enzymatically without use of a natural template, are included under the term "segments of DNA". Such synthetic DNA will be considered as derived from the species of organism that contains the analagous gene."

Two additional comments:

1) Synthetic polydeoxynucleotides that code for non-translated RNA (e.g., tRNA's), or for regulatory signals, or for no known natural product were intentionally excluded from designation as "synthetic genes".

2) For later parts of the guidelines, synthetic genes should be considered equivalent to cloned DNA segments in terms of purity.

Sincerely,

Daniel Nathans

Daniel Nathans

DN/lc

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Medicine

December 20, 1977

Donald S. Fredrickson, M.D.
Director
DHEW, PHS
N.I.H., Bldg. 1, Rm. 124
Bethesda, MD 20014

Dear Don:

Paul Berg has sent me a copy of his recent letter to you containing his modified definition of recombinant DNA which includes synthetic genes. While I agree with his definition, I do not agree with the proposal in his letter to handle synthetic genes at the same level of containment as purified DNA from the natural source.

The original rationale for requiring higher containment levels for work with recombinant molecules that carry natural DNA from higher mammals was that genetic material from humans and other primates might be more likely to contain viruses capable of producing human disease. So far as synthetic genes are concerned, there is no reason whatsoever for requiring higher containment levels for work with an entirely synthetic human insulin gene, for example, than for work with a synthetic gene for pig or fish insulin. Yet, this is precisely the effect of Paul's proposal.

I urge that the revised Guidelines deal with this problem by stating that synthetic genes (which represent the highest degree of purity imaginable), can be handled at the same level of containment used for purified DNA from lower eukaryotes, such as Drosophila, sea urchins, etc., provided that the synthetic genes do not code for known toxins. Any possible biohazard related to work with such genes would result from the "novelty" of their introduction into an organism such as E. coli, and the "novelty" factor should be no different so far as E. coli is concerned whether the sequence is that of fish insulin, porcine insulin, bovine insulin, or human insulin.

I have discussed this point with Paul Berg and he agrees with the arguments I've put forth.

I hope that you will deal with this matter in your revision of the Guidelines.

With best wishes,

Sincerely yours,

Stanley N. Cohen, M.D.
Professor of Medicine and
Professor of Genetics

SNC:seh
cc Paul Berg
Maxine Singer

THE UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL

DEPARTMENT OF HUMAN GENETICS
1137 E. CATHERINE STREET
ANN ARBOR, MICHIGAN
48109

TELEPHONE:
ANN ARBOR, 764-5490

December 20, 1977

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

Your performance as chairman was virtuoso.

As I attempted rather inadequately to convey in my closing remarks, one of my principal concerns is the articulation of these guidelines with the larger issue posed by the whole sweep of investigation concerning recombinant DNA. In this connection, you might be aware of certain "dynamic tensions" within the genetic community, stemming from the intellectual arrogance of the molecular geneticist, flushed with the astounding successes of reductionist biology, as contrasted (I hope) with a greater measure of humility on the part of those of us who are man-oriented, determined from the lessons of the past to make our progress carefully.

I had viewed the Science note and Asilomar as the first indications of real stirrings of conscience, a realization of the complexity of the Pandora's box the molecular geneticist had opened. For Jim Watson to repudiate that so completely, with no effective challenge from his peers, was a rather depressing red flag, upon which I have now had the opportunity to reflect. In effect, he said, 'we lost our nerve for a minute, please excuse the momentary lapse, but now just get out of our way.' I personally found that rather disturbing, to the extent that I considered asking to be excused from your Committee and appearing as a public witness on the last afternoon of our meeting. I am afraid the fact that I hadn't decided which way to go until I began to speak was reflected in a certain confusion in my Committee member's remarks.

With this lengthy preamble, let me again express the hope that somehow either the forwarding statement or the introduction to the guidelines themselves will reflect our awareness of the larger issues to which the guidelines relate. I really don't want to muddy the waters, but only to help ensure the necessary perspective. In this same vein, I wonder about retitling those guidelines: "Recombinant DNA Research, with Particular Reference to Lower Eukaryotes." This would then set the stage for the inevitable companion document, to be entitled "Recombinant DNA Research, With Particular Reference to Higher Eukaryotes."

The document itself of course, has to be quite technical, and here I would defer in judgement to the persons in the field and the legal types who

are familiar with the problems in implementing such a document (in which connection, I am sure that this document will shortly become a regulation rather than a guideline).

Now for a few quick technical comments.

1. Somehow industry must be brought into these guidelines, which will presumably be accomplished if they become regulations.

2. If they do become regulations, then, as brought out by a number of your witnesses, procedural aspects of the guidelines will need to be clarified.

3. I don't believe P1, K1 research needs to be included within the guidelines.

4. I favor giving the Director the authority to grant certain exemptions to the guidelines.

5. While it may be understood, it might be well to specify periodic re-evaluation of the guidelines.

I trust the skiing was all that you had hoped for.

Best regards,

James V. Neel, M.D.
Lee R. Dice University Professor

December 21, 1977

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

As an "unemployed" Bio-Medical Engineer ...
certified and top ranked for such position vacancies as those of Safety Manager at the National Institutes of Health, Grants Associate, and Health Scientist Administrator ...
having been in attendance throughout your recent two-day Director's Advisory Committee public meeting on the recombinant DNA SAFETY issue where, thanks to you, I was allowed a few minutes as unsolicited witness to deliver and to expand on my voluntary written statement of comments and recommendations for comprehensive management of bio-lab safety ...

I want to put, now, down in writing some additional impressions and recommendations for your personal consideration, as follows:

1. In general, there has always been and there still seems to be a wide disarray of unity in purpose and in action for the regulation and for the enforcement of BIO-LAB ENVIRONMENTAL SAFETY ... to say nothing about, additional, contemplated biohazards from recombinant DNA's.

2. In particular, turning now to that latter and additional aspect of this lingering problem, it appeared to me, at first, quite unreasonable that some public discontent with assurances for safety has risen to a stage where a Court injunction is being thought to halt the NIH from conductind research with what might be quite safe materials.

3. I can see now, however, that what evolved to this stage may be due to the "inadvertance" that ... in spite of the fact that the NIH Director has no statutory duties to regulate the ENVIRONMENTAL SAFETY of any extramural research operation, and in spite of the fact that the NIH Director does not, apparently, even intend to be such safety regulator ... the title of the present GUIDELINES is misleading, and their internal application to intramural NIH research is mentioned nowhere.

4. Therefore, to unburden the NIH from its misinterpreted and undesired regulatory involvement, I suggest that the title of the Guidelines be changed, as soon as possible, to:

ENVIRONMENTAL SAFETY GUIDELINES FOR INTRAMURAL RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH, WHENEVER RECOMBINANT DNA's ARE MADE OR EMPLOYED.

5. Furtheremore, I suggest that the Guidelines include, at least, an information-flow-block-diagram, such as the one I have proposed already to you and to your Committee, so as to provide a MODEL of Intramural NIH Biohazards Control System for possible adaptations by concerned research entrepreneurs and concerned regulatory agencies.

6. Moreover, and for similar reasons, I suggest that the Guidelines include in the Part on Roles and Responsibilities ... job descriptions for an Intramural Safety Manager and for an Intramural Safety Officer, indicating also their separate roles and responsibilities as Ex-Officio Members on the Intramural NIH Biohazards Committee.

7. In conclusion, I believe that once such MODELS of Intramural NIH Safety provisions will get published ... the present objectors may then withdraw their pleas for an injunction, and the long awaited begining of risk assessment experiments with recombinant DNA's in Intramural NIH High Containment Research Facilities will receive their endorsement.

Thank you.

Sincerely yours,

Naum S. Bers, Ph.D.
P.O. Box 1692
Rockville, Maryland 20850

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* I am an applicant for a career position with the NIH.

30 Barefoot Hill Road
Sharon, Massachusetts 02067

21 December 1977

Donald S. Fredrickson, M.D.
Director, National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Doctor Fredrickson:

I want to thank you for the opportunity to address the N.I.H. Recombinant DNA Molecule Program Advisory Committee.

As I indicated Thursday, 15 December 1977, I am the Biohazard Assessment Officer at the Massachusetts Institute of Technology, and a consultant to the Biohazard Safety Office at Harvard University. My association with M.I.T. began on 1 March 1977, and at Harvard on 1 July 1977. Prior to this I was a clinical microbiologist at Lederle Laboratories, and a member of their recombinant DNA committee. I have enclosed a copy of my curriculum vitae which describes my background in the biological sciences.

At the Massachusetts Institute of Technology my major responsibility is to develop a service oriented department, dedicated to biohazard control. The impressions and insights that I have developed as a result of interviewing and meeting with researchers and the public proved to be of uncalculatable value, as I have attempted to establish my presence at M.I.T.

It is not my intention to try and impress you. I merely want to indicate that the comments that I offer concerning the draft revised guidelines are based on many months of reviewing M.U.A.'s, interaction with the City of Cambridge Biohazard Committee, and discussions on recombinant DNA with scientists, both from my Institution as well as other Institutions in the country.

General Comments:

1) I agree whole heartily with the new definition of recombinant DNA.

2) I would exempt all P-1 experiments from the Guidelines.

3) I feel that the exemption clause is vital if meaningful risk assessment experiments are to be initiated in a reasonable period of time.

4) In general, I am in favor of downgrading the containment classifications. I feel that the draft revision is too stringent in the viral and plant sections.

5) I believe that political factors have influenced the Recombinant DNA Advisory Group to the point of obscuring scientific judgement. I am refering to the

statement on page 49597, "Nevertheless, the revised guidelines continue to be deliberately restrictive, with the intent of erring on the side of caution". In the absense of any supporting evidence that would indicate that recombinant DNA research is hazardous (or even potentially hazardous), the approach of erring on the side of caution may be counterproductive, be perpetuating public hysteria.

6) Based upon the available information, E. coli, K-12, is not an epidemic pathogen, and therefore is a suitable host for recombinant DNA research.

7) I am opposed to the idea that we need to develop many alternative hosts. Because our knowledge concerning both the genetics and biology of the proposed alternate hosts is primitive by comparison to E. coli, I would be forced to reevaluate my position on the potential risks associated with recombinant DNA research.

8) I do not see the justification or the requirement for 3 EK-2 lambda host vector systems, nor do I see the logic in having a growing list of plasmids approved for use with χ1776. If it turns out that one is required by law to monitor personnel and/or the environment for the release of recombinant DNA materials, the larger the number of systems certified for use will compound the problem. I must point out that in the City of Cambridge the Cambridge Ordinance requires monitoring. (Monitoring the release of recombinant DNA materials and its survival in the laboratory worker.)

9) I would suggest that caution be used, I am refering to page 19604, when describing the duties of the Biological Saefty Officer, I would change the statement, Subsection i, as follows, "verification that all recombinant DNA research personnel, etc.", be substituted for, "verification that all research personnel, etc.". The reason for this comment is that I do not believe that the N.I.H. intended to include all research with microbiological materials as the responsibility of the Biological Saefty Officer at this point in time. While I am not opposed to Biohazard Safety Officer involvement in other areas, I would suggest that since the document relates to recombinant DNA research that it should be stated accordingly.

10) The Recombinant DNA Advisory Group should determine an appropriate certification mechanism for the determination of investigator competency. In the absence of a standardized test, political considerations, both internal and external, will determine which Institutions require demonstrative proficiency on the part of investigators. It is conceivable that Institutions with rigid requirements will suffer from investigator migration.

11) Since the N.I.H. requires Institutions with P-3 or P-4 facilities to have a Biological Safety Officer and that all Institutions involved in recombinant DNA research provide medical monitoring and surveillance as well as an administrative structure for processing applications, the N.I.H. should provide a mechanism for defraying the cost associated with these activities. There are at least two mechanisms for defraying these costs; (1) the direct cost section on grant application could include a section on safety, or (2), Institutions could be

allowed to renegotiate an increase in the overhead rate. A small percent increase should amply cover the cost for providing the monitoring and medical resources associated with that given project.

12) The N.I.H. should request all Institutions which receive N.I.H. funds to develop a laboratory course for all incoming students.*

13) I would recommend that the Recombinant DNA Advisory Committee review the issues very carefully. If on the basis of scientific judgement the Recombinant DNA Advisory Committee concludes that recombinant DNA research is sufficiently hazardous, (or potentially hazardous) such that the draft revisions are appropriate, I would suggest that the N.I.H. set up a panel to consider the potential hazard aspects of research with microbiological agents in general, including etiologic agents. If recombinant DNA research is potentially hazardous, and therefore requires careful monitoring, then why not exhibit the same concern for Class I and Class II bacterial, viral or fungal agents? If E. coli K-12, is a potential pathogen, what then are Pseudomonas, Serratia, Proteus, Enterobacter, Influenza viruses, etc.?

14) The available data indicates that recombinant DNA research (like most microbiological research performed in the laboratory) represents an occupational risk. This point is even supported by Professor Jonathan King (M.I.T.). In his testimony on 15 December 1977 he indicated that he was not concerned about epidemics with K-12, and that he felt that the laboratory worker was at risk. If this is true, and I believe that it is, then how do we protect laboratory workers from potentially hazardous situations? Containment facilities are designed to protect the environment, not the investigator. Investigators must rely on containment equipment, and on technique to protect themselves. It seems counterproductive (and very costly) to me to go through the expense of facility renovation, or the construction of new facilities, if this effort does not alter the occupational exposure/risk. The broader use of the safer strains (EK-2) can have an impact on occupational exposure (i.e., P-4, EK-1 $\longrightarrow$ P-3, EK-2; P-3, EK-1 $\longrightarrow$ P-2, EK-2).

15) The N.I.H. should review the status of risk assessment experiment. In addition to the Martin-Rowe polyoma study, experiments which test the efficacy of containment should be initiated.

16) I would request the director of the N.I.H. request all Institutions that receive N.I.H. funding to require the Institutional Biohazard Committees review all recombinant DNA applications regardless of source of support (N.S.F., A.C.S., N.I.H., or Industry).* This would eliminate the possibility of investigators performing recombinant DNA research without the knowledge of the administrative structure of the Institution.

* I realize that the N.I.H. does not have the authority to require that Institutions initiate these actions. However, requests from the N.I.H. in these areas will encourage Institutions to consider these points.

I want to thank you for the opportunity to comment. If you have any questions or comments about the statements I have made, please do not hesitate to contact me.

Respectfully yours,

Dan Liberman

Daniel F. Liberman, Ph.D.

Enclosure

CALIFORNIA MEDICAL ASSOCIATION

731 Market Street / San Francisco, California 94103 / 415·777-2000

December 23, 1977

Donald S. Frederickson, M.D., Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Doctor Frederickson: Don

I am chairman of a committee of the California Medical Association titled the Committee on Evolving Trends in Society Affecting Life. Among its various interests and activities, the Committee had the responsibility for recommending a policy position to the California Medical Association on the question of Recombinant DNA. Following its review of the available material, including the NIH Guidelines, the Committee recommended support of the NIH Guidelines, with the further recommendation that such Guidelines be expanded to apply to DNA research conducted in private industry. The Council of the California Medical Association approved the Committee's recommendation.

Now that the NIH Environmental Impact Statement has been released, I would appreciate receiving 15 copies of Parts One and Two for the Committee's further review.

Sincerely,

Laurens P. White, M.D., Chairman
Committee on Evolving Trends in
Society Affecting Life

LPW:sd

Best wishes to you - Still pushing cigars

BACTERIAL PHYSIOLOGY UNIT
HARVARD MEDICAL SCHOOL

BERNARD D. DAVIS, M.D.
ADELE LEHMAN PROFESSOR
OF BACTERIAL PHYSIOLOGY

BOSTON, MASSACHUSETTS 02115
TELEPHONE: (617) ~~734-8900~~
732-2022

December 23, 1977

Dr. Donald Fredrickson
NIH
Bethesda, Maryland 20014

Dear Don:

I was grateful for the opportunity to testify before your Advisory Committee on the proposed revisions in the recombinant DNA guidelines, and I hope my remarks were useful.

I was asked to provide supplementary information on the benefits to be expected from research with this new technology. I have summarized these briefly on the first page the enclosed paper from the American Scientist, and I think it would be of little help to expand this material, although I could make many more extensive guesses. It might be of value to distribute the whole paper to the members of the committee, since some of them must wonder how scientists in the field can have become so much less apprehensive than they were initially, and this paper attempts, among other things, to explain why excessive anxiety was aroused at the beginning.

I would like to take the liberty of making a suggestion regarding further committees that might be considering later revisions. The present committee had only one microbiologist out of seventeen members, and he was a virologist rather than an expert on enteric bacteria. Since the key issues turn out, again and again, to hinge on technical questions in infectious disease, it seems to be that the presence of several experts in infectious disease and particularly enteric infections might have helped to correct erroneous statements that crept into the discussion. There were quite a few such statements at last week's meeting, which necessarily went unchallenged.

One additional point. Some committee members were no doubt shocked by Jim Watson's statement that he would allow investigators to carry out any experiments they wished with recombinant DNA, without regulations. Without qualifications, this statement must seem irresponsible to an outsider. I subsequently asked Dr. Watson whether he would not expect that any investigator dealing with a hazardous source of DNA, such as a toxigenic bacterium, would treat that material and the recombinant with the usual precautions for dealing with such pathogenic organisms. He said, "of course --- that's just common sense".

So it is clear that what he meant, in his elliptical statement, was that investigators should handle known dangerous organisms with caution, but this is what they have always been trusted to do; recombinant DNA injects no new significant element in the situation.

If I may be of any further help to you please do not hesitate to call on me.

Sincerely,

Bernard D. Davis

BDD:hrg

[Enclosure was The Recombinant DNA Scenarios: Andromeda Strain, Chimera, and Golem, Bernard D. Davis. Am. Sci., 65:547-555, Sept.-Oct. 1977.]

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

December 27, 1977

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Thank you for giving me the opportunity to participate in the special meeting of the Advisory Committee to the Director, NIH, on December 15-16. I was impressed by the clear and forceful presentation of dissenting views, made possible by the diverse interests represented by the participating witnesses. The revised Guidelines appear to steer a cautious middle course which is advisable, given our present knowledge.

From my testimony you will note that the experiments of direct concern to my research group, cloning of the Agrobacterium Ti plasmid in E. coli, have been placed in a curious situation by the proposed revised Guidelines. They could be considered candidates for the list of experiments excluded from the Guidelines. (I have criticized the vagueness of the criteria stated for defining what is non-novel recombinant DNA.) On the other hand, such experiments, if judged to involve novel recombinant DNA, must be performed under P3EK2 containment. This is a higher level of containment than is presently required: P2EK2. Neither alternative seems appropriate. Because we do not yet understand the mechanism by which part of the Ti plasmid is incorporated into eukaryotic (plant) cells, we do not know how to judge the safety of Ti plasmid fragments. I believe it is therefore premature to place our cloning experiments outside the Guidelines at this time. The evidence available thus far indicates that the Ti plasmid does not function in E. coli. I have submitted a statement from Jeff Schell which summarizes the evidence that E. coli containing the whole Ti plasmid does not incite plant tumors. Nevertheless, in the spirit of "erring on the side of caution," I recommend keeping these experiments under the Guidelines.

On the other hand, elevating the level of containment to P3EK2 seems most unreasonable; a containment level of P2EK2 would be acceptable, and P2EK1 would be preferable. I would recommend lowering the level of containment slightly (to P2EK1) on the basis of our experience with the clones containing Ti plasmid fragments. These strains fail to incite plant tumors, although they contain all or most of the portion of the Ti plasmid which

can transfer to the plant cell. Even when the whole Ti plasmid is put into E. coli the strain cannot incite plant tumors. The possibility of creating a super-pathogen by our cloning experiments thus appears nil.

I hope that these facts will be considered and that the containment level for cloning Ti plasmid fragments will be set at a reasonable and clear position before the revised Guidelines are accepted. I thank you for the opportunity of stating our dilemma publicly. It was a pleasure and a privilege to participate in your committee meeting.

Sincerely yours,

Mary-Dell Chilton

Mary-Dell Chilton
Research Associate Professor
Department of Microbiology & Immunology
SC42

Testimony of Mary-Dell Chilton

Introduction Section

I favor the idea of excluding certain recombinant DNA experiments from regulation by the Guidelines. By excluding from consideration a large number of experiments which are innocuous, we focus attention on the more critical issues, where it properly belongs. However two questions are not clearly answered by the statements in the Introduction defining what is meant by the term "novel recombinant DNA".

1. Two apparently alternative criteria are stated for judging the novelty of a recombinant DNA molecule. Must it be non-novel by both criteria in order to be eligible for exclusion from the Guidelines, or is either criterion sufficient? A case in point occurs in the research in which I am involved: cloning of the Agrobacterium Ti plasmids in E. coli. Experiments in the laboratory of Dr. Jeff Schell, State University, Ghent, Belgium (see appended signed statement) have shown that the Ti plasmids can be transmitted to E. coli from Agrobacterium by conjugation, and that the Ti plasmid can replicate in E. coli, although it does so only poorly. Thus cloning Ti plasmid DNA in E. coli involves a "combination of DNAs...derived from genomes known to replicate within the organism used to propagate the recombinant DNA," and such recombinant DNA could be considered non-novel. However such recombinant DNA is novel according to the other stated criterion, for it does "consist of segments

of...DNA from different species that are not known to exchange chromosomal DNA by natural physiological processes." This ambiguity in the definition of novel recombinant DNA could be clarified by deleting the word chromosomal from the foregoing statement. Alternatively, it should be stated clearly whether either criterion suffices, or whether both must be fulfilled.

2. It is stated that the Director of NIH...shall prepare the list of those combinations of DNAs...which are not considered novel for this purpose and are therefore not covered by these Guidelines. Will any other criteria be employed in deciding which combinations are placed on the list? If so, the criteria which may be invoked should be mentioned here for clarity. For example would the pathogenicity of the organism used as host be of additional concern? Would the conjugative promiscuity of the plasmid used as vector be considered? (For example, would RP4, a highly promiscuous conjugative plasmid, be listed as a safe cloning vehicle for any of the wide range of bacteria into which it can be transmitted by conjugation?)

In my opinion, some of the recombinant DNAs which would fulfil the criteria for exclusion stated explicitly here should nevertheless remain under the guidelines. As a specific example, the cloning of Agrobacterium Ti plasmid in E. coli should, despite the definition, be considered novel recombinant DNA for the present until the properties of such recombinant DNA have been assessed

carefully. I would like to see considerable clarification, for the benefit of scientists as well as the public, of what range of experiments we can now expect to find listed as outside the Guidelines. I support strongly the idea of excluding many experiments which are generally regarded as safe. However I would hope that careful consideration will be given to any potential unusual hazard of recombinant DNA before judging it to be non-novel.

Experimental Guidelines

The clarification afforded by the alterations in categories in these revised Experimental Guidelines is excellent. The distinction between polypeptide toxins and other toxins is especially valuable. In general I support the revised Experimental Guidelines. Two items are in need of more consideration, and the sections dealing with them should be revised:

1. Containment for cloning DNA from plant pathogenic bacteria. The treatment of cloning experiments involving DNA from plant pathogenic bacteria in these revised Guidelines is not reasonable. The containment level required for all such experiments is P3EK2. This requirement fails to take into account differences in the economic importance and geographical domain of various bacterially caused plant diseases. A classification of plant pathogenic bacteria was recently proposed by

Drs. Kado, Panopoulos, Shepherd and Bruening in a letter to the Director of NIH. These plant pathologists recommend no containment higher than P2EK2 for the cloning of DNA from plant pathogenic bacteria. This places such cloning experiments at the same level of containment as those involving plant viral genomes. I would strongly urge that the level of containment for cloning DNA from plant pathogenic bacteria be set at P2EK2. The only experiment of this type currently being performed to my knowledge is the cloning of Agrobacterium Ti plasmid DNA, an experiment which was explicitly designated P2EK2 in the previous Guidelines. It would be particularly ironic for these cloning studies to be the only experiment whose containment level is elevated in the revised Guidelines: studies of the natural genetic engineering potential of these Ti plasmids are cited as part of the justification for general decrease in containment of recombinant DNA experiments.

2. Handling of Recombinant DNA. The Guidelines dictate that novel recombinant DNA be handled with "good microbiological techniques equivalent to those in a P1 laboratory." The implication is that novel recombinant DNA which comes from a P4 level cloning experiment can be disinfected (for example, mixed with a phenolic agent, a step commonly used in the isolation of biologically active transforming DNA!) and poured down the sink. Transformation of several species of bacteria can occur

in nature. It seems to me that the procedures recommended by the Guidelines allow a reasonable possibility of escape of novel recombinant DNA. Until data are available which assess the probability of such escape, precautions should be taken to inactivate transforming activity before discarding samples of novel recombinant DNA. Treatment with bleach or acid or dry heat should be required for decontamination of glassware. Waste materials such as gels and plastic implements should be incinerated. Autoclaving is not satisfactory, for DNA can reassociate to form native molecules (active in transformation) during the slow cooling process.

Statement

On the in vivo transfer of the Ti-plasmid from A.tumefaciens to E.coli

It was observed in the laboratory for Genetics, State University, Gent, that the Ti-plasmids from A.tumefaciens can be naturally transferred to E.coli.
Two different mechanisms can promote these DNA transfers :

1°) Mobilisation by the wide host-range P-type plasmid RP4.
It is a well documented fact that RP4 is very readily transferred and replicates well in various Agrobacterium strains. It was furthermore observed that co-integrated plasmids consisting of complete RP4 DNA and complete Ti-DNA parts, are formed spontaneously at frequencies of 10^{-5} to 10^{-3} (i.e. one out of 10^3 to 10^5 cells harbouring both plasmid types in fact contain the Ti::RP4 co-integrated plasmid).
Some of these co-integrated plasmids still convey oncogenicity when present in an Agrobacterium host. These plasmids appear to have the wide host-range of the RP4 plasmid since they have been shown to transfer at a high frequency ($>10^{-2}$) to E.coli K12 r^-m^- hosts.
In E.coli the co-integrated Ti::RP4 plasmid replicates well but can be shown to dissociate frequently (1-10%) into RP4 and Ti plasmids where upon the Ti-plasmid appears to be lost.
The oncogenicity of E.coli (Ti::RP4) strains has been extensively tested on pea-seedling-sunflower hypocotyls and tobacco leaves and stems. At least ten different cultures were tested on each of these plants. In no case was there any evidence of crown-gall formation or any other form of pathogenicity. The tested E.coli (Ti::RP4) strains were subsequently shown to still harbour the complete Ti::RP4 co-integrate by crossing them with plasmid-free Agrobacterium C58-C1. The Agrobacterium transconjugants were shown to be fully oncogenic.

2°) Transfer constitutive mutants of the Ti-plasmid have been isolated and the Tn1 transposon (conferring resistance to Ampicilline) has been introduced in this Ti tra^c plasmid yielding Titra^c::Tn1 plasmids. Some of these plasmids have been shown to be normally oncogenic in Agrobacterium. When crossed with E.coliK12 r^-m^- it can be shown that conjugation takes place since the Tn1 marker is transferred from Agrobacterium to E.coli with a frequency of 10^{-3} to 10^{-4}. However, the transconjugant cells, behave as "abortive transconjugants" since the ampicilline resistant E.coli colonies observed have been shown to contain only about 5-10 Ampicilline resistant cells. This indicates that the Ti-plasmid replicates very, very poorly in E.coli. Oncogenicity tests on pea-seedlings, sunflower hypocotyls and potato discs were invariably negative.

M. Holsters
1.

STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOLOGICAL SCIENCES

December 27, 1977

Dr. Donald Fredrickson
Office of the Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing to convey a few impressions of the December 15-16 Advisory Committee Meeting. Specifically, I wish (1) to discuss some instances where I found the material presented by some witnesses to be incomplete and potentially misleading and (2) to expand on my remark about the current absence of a valid theoretical basis for ascribing special "potential hazards" to recombinant DNA research.

1. Relevance to recombinant DNA.

One recurrent feature of many presentations was that their specific relevance, if any, to recombinant DNA research was not made explicit. These include, for example, Jon King's concerns about laboratory infections by coliform bacteria entering the body by routes other than oral. Coupled with his assertion that he does not fear epidemic spread and the general presumption that only very rare recombinants might be harmful, this seems to make DNA recombinants far safer than ordinary class 2 pathogens, for example. Likewise, Dr. Suzuki's discussion of applications and misapplications of science seemed to imply that recombinant DNA work was somehow more susceptible to misuse than classical genetic studies of temperature sensitive fruitflies, for instance. I hope he can be urged to spell out his reasons for that belief.

2. The question of novelty.

Besides these more blatant examples, there were frequent statements that reflected a failure to distinguish between those hazards attributable to artificial recombination and those that are already inherent in all biological experimentation (or indeed in any activity, experimental or not, that influences the growth and reproduction of living organisms). As I consider this issue central to the main point of this letter, let me cite one example from the Advisory Committee meeting. In the discussion of the Introduction section, someone (Mr. Helms, I believe) summarized our committee's action in excluding non-novel recombinants with words to the effect that "If it's not novel, it's not dangerous." Miss Zimmring, on the other hand, reiterated the statement in Document 25 p. 71 that "The real question is not whether the organism is novel, but whether it is safe."

While the statement that everything non-novel is safe might seem supportive of our proposed revisions, it is in fact not the rationale for them and cannot be logically defended. We are all aware that the world is full of natural biological objects, untouched by molecular biologists, that constitute actual or potential hazards to human health or ecological stability. Natural as well as artificial genetic variation may either enhance or decrease the hazards in any particular case. The proper questions are therefore not whether DNA recombinants are safe but rather (1) whether bacteria carrying recombinant DNA are, as a class, less safe than bacteria picked at random from soil or sewage and (2) where specific DNA recombinants might pose any hazard, whether the risks involved differ significantly in degree or in kind from natural biohazards that are successfully handled by conventional methods. Where there is no novelty, the answer at least to the second question must certainly be negative; because whatever hazards might exist are with us already, and we can hardly protect the environment by trying to contain completely things that are already occurring naturally all the time.

3. Are DNA recombinants expected to be dangerous?

The reasons for worrying about hazards can fall into two categories: (1) direct evidence (e.g., thalidomide causes birth defects in humans; DDT is bad for pelicans) and (2) indirect arguments, that constitute reasonable extrapolations of existing data. A good current example of an indirect argument is the relation of fluorocarbon aerosols to the ozone layer. There is no direct evidence that the ozone layer has in fact been affected. But a great deal of hard chemistry backs up the prediction that damage to the ozone layer is a reasonable expectation. Another example is the effect on mankind of increasing the level of background irradiation. Below a certain level, no harm has been observed. We cannot point to any specific corpses as identified victims of low level radiation. But if we consider available data on humans at high doses, and animals and bacteria at low doses, in conjunction with physical and biochemical information on the mechanism of interaction of radiation with living cells we have reasonable cause for concern.

The absence of direct evidence that recombinant DNA is harmful has been frequently mentioned, by Jim Watson among others. One can of course try to extend this data base still further, as is being done. However, many other human activities resemble recombinant DNA research in their apparent freedom from significant danger. Society does not routinely respond to every apparently harmless activity by demanding more extensive risk assessment data. Why is artificial recombinant DNA treated differently?

I believe that one reason is a lingering misimpression dating back to Asilomar that someone did have a valid, perhaps profound, indirect argument, based on preexisting data or preestablished concepts from genetics, biochemistry, virology, epidemiology or evolutionary biology, that in some way predicted that artificial recombinants were more likely to be hazardous than natural organisms; i.e., that the potential hazards of organisms with recombinant DNA were somehow more "potential" than those that are already inherent in living on a planet inhabited by other species of living organisms capable of natural variation.

Such an indirect argument might be very specific, like the possibility of cloning a latent virus during a shotgun experiment; or very general, like the notion that among the array of recombinants cloned there will be some that disrupt the balance of nature. Either type of argument might justify special precautions for recombinant DNA research, provided it is spelled out in a form sufficiently explicit so that one can analyze it step by step and see whether one agrees with the assumptions and the logic.

Jim Watson summarized the situation with respect to his own specific concern at the time of the moratorium - that of disseminating latent tumor viruses - and pointed out that the whole idea really didn't make sense when subjected to further analysis. Note that this is something quite different from the numerous allegations that recent data have diminished some people's fears about recombinant DNA. As I understood him, Jim was saying that his initial idea was basically a dumb one; that what was mainly needed was more thought, not more data. At any rate, this is a good example of a specific indirect argument that failed to pan out.

On a much more abstract level, there is the general notion that, even though the typical DNA recombinant that turns up in a shotgun experiment is probably unable to survive in competition with natural organisms, exceptional recombinants may be even more fit than wild bacteria; and that if molecular biologists do enough cloning, they will eventually encounter such exceptions. The argument can be extended, as it was at Falmouth, to say that, even if all K-12 recombinants are unfit, there is a small chance that the cloned DNA will be transferred out of K-12 into some more robust bacterial strain, which the cloned DNA would render even more fit than it had been. Among these rare recombinants that are positively selected, some might have undesirable properties. Thus one can argue that the risk, however small, is not zero; especially as the magnitude of the "undesirable properties" is undefined.

The problem with this reasoning, if evaluated as serious scientific theory, is that it does not address the control situation at all; i.e., it never asks whether the expected rate at which disruptive gene combinations might arise in recombinant DNA research is greater than their rate of origin by natural genetic variation in bacterial populations untouched by human hands. I don't see this question as in any sense trivial; and if anyone else does, I hope I can one day be enlightened as to why. It's clearly true that, if I grow a bacterium harboring cloned DNA from a shotgun experiment, that bacterium might harbor gene combinations which, when transferred to some other bacterium, might convert the second bacterium into a pest or pathogen. But it's also true that, if I pick a random bacterium from the nearest sewer,that bacterium might harbor a natural plasmid which, when transferred to some other bacterium, might have the same result. In that second (natural) case, one can argue that most such transfers generate bacterial types that have already appeared, so that only a few plasmids arising as fresh mutants or recombinants would generate new problems; but that limitation is counterbalanced by the fact that a bacterial plasmid is much more likely to function in harmony with the recipient bacterium than a gene from some more distant source. It ends up as a draw, at least at present. (The fact that combinations from very distant sources are on the one hand more novel and on the other hand less likely to succeed than combinations from more closely related species has in fact led to some inconsistencies in the present Guidelines;

and I believe you can find examples on your transcript of the meeting where different individuals make exactly opposite estimates of relative risks for this reason.) At any rate, whenever we reach the point where the discussion of risks does not concern the object at hand but rather some possible product several steps removed from it, we must ask whether the concern is really recombinant DNA rather than simply the vagaries of the natural genetic lottery.

Now obviously these two examples do not prove that recombinant DNA research is safe; nor even that a good theoretical argument for danger cannot be made. I'm just saying that, either such an argument has not yet been made, or else I have not yet seen it or understood it. Perhaps some pastiche of the public statements of Paul Berg, George Wald and Bob Sinsheimer could be composed that already constitutes such an argument to intellects more perceptive than my own. But as years pass and nothing appears that is laid out in a form that I can analyze, I have increasing doubts that anything is really there. (Part of the problem is that most of what has been said to date consists of rather informal statements, which the listener or reader must formalize for himself if he is to take them seriously. Thus, while Jim Watson's concerns about latent tumor viruses may have been unfounded, perhaps other individuals were making different assumptions about the same material, and perhaps their concerns do warrant our attention. Until they spell out their assumptions in detail, I'll never know for sure. Similarly, I feel that much of the discussion at Asilomar ignored the role of natural selection that has since been forcefully emphasized by Bernie Davis. I don't know just what was in the back of other people's minds, but very little of what surfaced indicated awareness of the fact that phages and plasmids put out into nature are not spreading into a ecological vacuum, as they can do in the laboratory, but rather are in direct competition with their natural counterparts in a world that is already saturated with phages and plasmids. This is not too surprising, in that molecular biologists don't spend too much time thinking about Malthusian equilibria and their implications. But in this area again, the main need was for more thought rather than for more data, and I personally derive more assurance from the general principles of population biology than from the specific results of feeding tests with E. coli K-12. I say this even though the one population biologist who attended the Falmouth conference and subsequently communicated about it to you (Bruce Levin) doesn't evidence much interest in the role of competition either (for reasons best known to himself).)

What I hear Bob Sinsheimer saying now, for instance, is mainly, "Artificial recombinants are new, and therefore might have unexpected properties, including bad ones." I agree completely with that; and if that was all that Asilomar was about, well and good. But that's a far different statement from the assertion that DNA recombinant research is expected to be hazardous. I've gone into all this at such length because I believe that many of the attitudes presently taken toward DNA recombinant research have been colored by the notion that there is such an expectation.

Certainly I don't blame the organizers of Asilomar for raising the issue without formalizing their fears into a serious theory. But I do find it noteworthy that, since Asilomar, neither experimental facts nor good theoretical arguments have been produced to reinforce those fears.

4. Hazards of biological research in general.

As I implied above that DNA recombinant research may be no more hazardous than biological research in general, I should make it explicit that I am not suggesting (as Jim Neel seemed to be doing) that there is a need for regulation of an even more extensive segment of research. I share with many scientists the rather parochial tendency to draw on different types of research for my comparisons, as though bacteriological research were the sole, or even a major, human activity that influences the growth and distribution of bacteria. But certainly the doctor who prescribes penicillin to a patient, the farmer who puts another acre of soil under cultivation, and the city that builds a new sewage disposal plant all have much greater impact in this respect than the research biologist does. I suspect that the total impact of all biological research activities is quite trivial, although there may be exceptions.

5. Burden of proof.

Finally, I must comment on Mr. Hutt's summary statement, in which he reiterated his viewpoint that the burden of proof must be on the scientist to prove that the research is safe, rather than on others to prove that it's dangerous. I'm not sure that I really understand his point (and may even be misstating it here). I suspect it's derived, to some extent, from other areas of practice - e.g., drug manufacturers must demonstrate the safety of their products by performing feeding tests to show they are not toxic; clothing manufacturers should test flame retardants for carcinogenesis, etc. In these areas, there is clear precedent for expecting danger, based on previous experience with other products, and standard tests are available to evaluate specific risks. With recombinant DNA research, neither of these conditions obtains. The risks if any are unknown. What passes for "risk assessment" tests various aspects of containment but does not deal directly with danger. I suspect that Mr. Hutt's viewpoint is colored by a residual impression that there is some a priori grounds for expecting the research to be dangerous, but I may be wrong. At the moment, the activities of molecular biologists seem to be judged by quite a different standard from those applied to the farmer, the doctor and the sanitary engineer mentioned in my previous paragraph.

I apologize for the length of this letter, and also for the fact that it does not consist of specific suggestions for the immediate task at hand. However, evaluation of the revisions to the Guidelines does require an assessment of the overall status of the questions that generated the Guidelines themselves.

Sincerely yours,

Allan Campbell
Professor of Biology

AC/an
cc: Jonathan King
David Suzuki
Dennis Helms
James Watson
Paul Berg
George Wald
Robert Sinsheimer
Bernard Davis
Peter Hutt
James Neel

AREA CODE 608
PHONE 262-2177

McARDLE LABORATORY
FOR CANCER RESEARCH
MEDICAL CENTER
UNIVERSITY OF WISCONSIN • MADISON, WISCONSIN 53706

December 28, 1977

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson,

Thank you for the opportunity to attend the December 15-16, 1977 Meeting of the Advisory Committee to the Director of N.I.H. and to address the members of this Committee. Since the imposed five-minute time limitations did not permit me to clearly express all data, let me remphasize two main requests I wanted to make:

1. Please implement as soon as possible, hopefully within the next few weeks, those parts of the new Guidelines proposal which modify the definitions of recombinant DNA and which exclude from under the Guidelines experiments between recombining or coexisting genomes, especially between the genes of E. coli K-12, its phages and plasmids. There was uniform agreement as to the latter provision and any further delays in implementing it would greatly interfere with proper functioning of the already overburdened N.I.H. Office of Recombinant DNA and with basic scientific research. I would like also to stress that on the basis of general media reports many scientists believe that recombinant DNA experiments between E. coli K-12 and its phages or plasmids are already outside the Guidelines. Thus, your prompt confirmation of that by any simple means should preclude any unnecessary future confusion and ensuing accusations similar to those experienced by the insulin team from the University of California at San Francisco. We already heard at your meeting that the research sponsored by the pharmaceutical industry applies the new version of the Guidelines, and my understanding is that they are legally correct.

2. Please exlude from the Guidelines most of the experiments employing EK1 or EK2 host-vector combinations which carry novel recombinant DNA, as specified in point 7 and justified in points 8-10 of my official testimony, a copy of which is enclosed. A few exceptions from this general exclusion could be specified in the new Guidelines, although they will be more of emotional than of any scientific and factual value.

In addition to the reasons specified in my enclosed testimony, there are also legal reasons why including all of the EK1 and EK2 novel DNA experiments into the new Guidelines is unjustified. The Recombinant DNA Advisory Committee and the ensuing Guidelines are based on Section 301 of

the Public Health Service Act (42 U.S.C.241), in which "the Secretary of the H.E.W. is directed to conduct research, investigation, demonstration and studies relating to the causes, diagnosis, treatment, control and prevention of physical diseases and impairments in man". Since no such "diseases and impairments" were ever demonstrated and since there is uniform agreement "that E. coli K-12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts", further restrictions on the EK1 and EK2 based research are contrary to the letter and spirit of the Public Health Service Act.

I would like to congratulate you on the way you conducted the hearings, especially with witnesses whose testimonies were mainly emotional or political. I was disturbed, however, with the precedent of providing an official, government-sponsored forum for as illogical and purely emotional testimony, as e.g., that of officially invited foreign witness Dr. David Suzuki, especially since his testimony was widely reported in the press. E.g., the report by Judy Randal of Princeton Features under the title "David Suzuki is a scientist with a conscience about DNA research" was carried in our local newspaper. In his testimony, which was much longer than the permitted five minutes, and which I admit was quite entertaining with a spellbounding and almost religious flavor, he developed a thesis that traditional genetic research as carried out by him is good and the use of the new recombinant DNA technique is evil because of his internment during World War II due to his Japanese heritage. Since ten years of my life were spent under Hitler and Stalin, I probably have as much if not more right to discuss racism and erroneous interpretations of eugenics and genetics applied by facist governments. However, the logic of connecting the events of the 1930's and 1940's with a new technique developed in the 1970's eludes me completely, unless it is purely a demagogical trick. I would greatly appreciate receiving from you the exact transcript of Dr. Suzuki's speech which might help me to understand the logic and motives behind his manifesto. Perhaps this would also help me in understanding the logic of regulating EK1 and EK2 based research to protect the public from imaginary hazards, for which there is uniform agreement that from the practical point of view they do not exist or could not even be postulated on the basis of present knowledge.

Please include this letter in the proceedings of the meeting.

I hope your skiing vacation in Europe was very pleasurable.

With best wishes for a very happy New Year,

Sincerely yours,

Waclaw Szybalski
Professor of Oncology

WS:kjd

Testimony of W. Szybalski at the Meeting of the Advisory Committee to the Director, N.I.H. (December 15-16, 1977).

Dr. Fredrickson, Members of the Advisory Committee:

My name is Waclaw Szybalski. I am a Professor of Oncology, University of Wisconsin Medical School. For three years I was a member of the Advisory Committee on Recombinant DNA, at the time that the present and the new proposed Guidelines were drafted. I am not carrying on any research which involves novel recombinant DNA.

1. We are gathered here because in 1974 several scientists were voicing concerns about the possibility of serious epidemics caused by E. coli K-12 carrying recombinant DNA.

2. At present, in December 1977, we know "that E. coli K-12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts", and there is uniform agreement about it among well-informed experts in the field of epidemiology and medical microbiology (see Memo NAR-89/1 in NARSM, May 15-July 15, 1977). This conclusion agrees completely with the experimental facts and with all that we know about the mechanisms of epidemics.

3. If the scientists who sounded the 1974 warning had been informed as well as we are now, no letter to "Science" would have been written, there would not have been any N.I.H. Guidelines for Recombinant DNA Research, and we would not have been here today.

4. So what should we do now with those parts of the Guidelines which are to protect us from imaginary dangers that we know are of no practical concern?

5. The Recombinant DNA Advisory Committee, of which I was a member, acted as Committees usually do, i.e., it acted conservatively in a politically cautious way, it took time, it worked hard and tried not to "rock the boat". The Committee took the following actions:

> (a) Combinations of DNA from those organisms which frequently recombine in nature were eliminated from the Guidelines. This was a wise and positive action, but not original, since it followed the legislative proposals of the U. S. Congress.
>
> (b) slight adjustments in the prescribed containments were made,
>
> (c) and most unusual, a new introduction was prepared stating that the "Guidelines continue to be deliberately restrictive with the intent of erring" on the side of caution (Federal Register, Sept. 27, 1977 p. 49597, column 1, the end of the third paragraph).

6. So how shall we comment on this new version of the "deliberately restrictive" Guidelines, still so much out of tune with the present assessment of the hypothetical risks as to be intentionally erroneous?

7. Let me make one major suggestion, which would render the Guidelines scientifically more sound, but still quite conservative. I suggest that with only a few exceptions, one should exclude from the Guidelines all experiments employing EK1 or EK2 host-vector combinations which carry novel recombinant DNA. If you think it would be helpful, you should require only a very simple registration of these EK1 or EK2 experiments. E. coli K-12 host-vector combinations carrying DNA coding for known polypeptide toxins could be among the experiments which would still remain under the Guidelines.

8. Let's face it: There is no trace of any practical risk in cloning and studying human genes coding for, for instance, immunoglobulins; - and these extemely important and beneficial studies on our natural defenses against diseases are made very cumbersome and often impossible under the Guidelines. I cannot comprehend why most important, safe and very beneficial medical research on human genes and proteins that are involved in controlling our health should be greatly restricted. I could give many examples how the various studies of cloned genes could be of great benefit to basic science, to health sciences and to protecting our endangered environment. E.g., within the last few months an important and unexpected discovery was made, namely it was found that smack in the middle of our blood protein genes there are naturally inserted special DNA sequences which are not translated into proteins.

To cite one more example, the recombinant DNA technique could have very beneficial impact on the production of safe and effective vaccines, especially since at present it is not possible to make vaccines against several important infectious diseases, e.g., Herpes II, which causes very painful, debilitating, dangerous and rather frequent disease, especially in women. The traditional approach, i.e., the use of directly killed Herpes II as vaccine would be very risky since there are strong indications that such inactivated virus may have a cancer-inducing potential. An appealing and safe way to proceed would be to try to produce pure antigens by the recombinant DNA technique. There is no indication of any practical risks in trying to produce a pure and safe vaccine by the recombinant DNA technique, but in most cases the Guidelines forbid it or make it rather impossible to do.

Dr. Fredrickson, if the Guidelines are not modified as to permit and even encourage such rewarding directions as pure and safe vaccine development we may be justly accused of contributing to human misery and disease, with one example being the Herpes II infection, which makes a woman not only miserable but also has been suggested as a predisposing cause of cervical cancer.

9. We as a nation will have to pay a very high, and totally unjust, price in diseases and misery which could be prevented, in lives not saved, in taxpayers' money (and I object as a U. S. taxpayer), in lost talents, in lost freedom of inquiry, in loss of respect for the N.I.H. regulations because some parts have no sound scientific basis, in misleading the Congress and public, and in misdirecting the environmental movements, among others. This all happens because the restrictive nature of the Guidelines misleads and frightens the layman who believes that the imposed restrictions indicate real dangers and not just imaginary risks.

10. And why shall we do it? In the name of the imaginary risks which we know now are of no practical concern, being something much less than <u>one</u> minor illness (maybe upset stomach) per 10,000 or 100,000 years of research in 10,000 or 100,000 laboratories?

Dr. Fredrickson, members of the Advisory Committee, I urge you emphatically to make a courageous and very sound decision, i.e., to exclude most of the EK1 and EK2 novel recombinant DNA experiments from the Guidelines, and perhaps just require these experiments to be simply registered with the N.I.H. Office of Recombinant DNA. I am honestly concerned that history may judge us very harshly, since some time from now it will be possible to calculate how many lives were unnecessarily lost, how much human misery was prolonged because of delays in beneficial research as imposed by the restrictive Guidelines and ensuing regulations.

I shall be glad to answer any questions and I would appreciate it if you would let me question other witnesses appearing here, if their statements should be in conflict with the known facts.

BACTERIAL PHYSIOLOGY UNIT
HARVARD MEDICAL SCHOOL

BERNARD D. DAVIS, M.D.
ADELE LEHMAN PROFESSOR
OF BACTERIAL PHYSIOLOGY

BOSTON, MASSACHUSETTS 02115
TELEPHONE: (617) ~~734-8800~~
732-2022

December 30, 1977

Dr. Donald Fredrickson
NIH
Bethesda, Maryland 20014

Dear Don:

If the transcript of my initial statement for your Advisory Committee on recombinant DNA has not already been prepared, it might save your staff some work, and produce a slightly better product, if the enclosed version could be used. This version contains all the material that I presented in my first statement, plus about 20% more for which there was not time.

May I thank you again for the opportunity to participate in that meeting.

Sincerely,

Bernard D. Davis

BDD:hrg
Enclosure

NIH Advisory Committee on Recombinant DNA

Testimony of Bernard D. Davis, M. D.

Harvard Medical School

December 15, 1977

Though I am not here as an official representative of the American Society of Microbiologists, my publications on recombinant DNA have led officers of that society to recommend me to serve here, and I believe the views that I shall present are widely held among microbiologists.

I am convinced that the alleged dangers from recombinant DNA research have been enormously exaggerated, on the basis of scenarios that depend on the compounding of many low probabilities. The proposed revisions are therefore a step in the right direction. On the basis of what we know today, a year and a half after the original guidelines, the following conclusions seem to me reasonable.

1) Except for the insertion of a gene for a potent toxin, the danger of creating a pathogen and causing a laboratory infection, by cloning DNA in E. coli K12, is very much less than the danger of working with everyday pathogens. Hence this danger is well within the range that has been left in the past, without substantial danger to society, to the prudence of microbiological investigators.

2) The danger of epidemic spread from the laboratory, in work with E. coli K12 and even more with its derivative EK2 strain, is virtually nil, because of the demonstrated incapacity of the organisms to colonize the gut and to transfer their plasmids to more viable organisms. This conclusion was offered a year ago on the basis of theoretical considerations; it is now amply supported by experimental evidence.

3) More specifically, the danger from shotgun experiments with DNA from eukaryotes, including human DNA, is not significant. This conclusion is based on the following considerations. a) Even if the tissue should contain genes of a tumor virus, the amount of foreign DNA incorporated into any recombinant strain would lead it to have only around one chance in a million of picking up those genes. b) If the tumor virus genes are rare in man, the chance of their pickup is small; while if they are common, they are already widespread and the increment provided by recombinant bacteria would not add significant danger. c) Viruses themselves are known to be more infectious than their free DNA, by many decimal orders of magnitude. I would consider work with SV40 virus, or with any other tumor virus, considerably more hazardous than work with E. coli containing the tumor virus DNA.

On scientific grounds, then, the original guidelines are far too severe, and the proposed revisions are more than justified. I would hope that further revisions will follow as experience mounts without casualties and public anxiety recedes. The public cannot be blamed for having a high level of anxiety at present, in the light of the many alarming statements that have been made by some scientists; but in time the public will surely catch up with the scientific realities.

One may ask how I can justify such an apparently extreme view, since responsible scientists within the field felt deep concern at the start and even recommended a moratorium on certain kinds of work. I believe the scientists were victims of a serious misunderstanding of the problem, arising with the best of intentions. Among the reasons for this misunderstanding we may cite the following.

1) The molecular biologists who initiated the problem exaggerated the role of genetic novelty in the evolutionary process, while ignoring the dominating role of natural selection in determining which novel genotypes spread and which are culled out. A novel artificial recombinant will not

spread in nature unless it can compete with the organisms that have been selected in the past for their adaptation to the environment.

2) The novelty of the proposed recombinants was also exaggerated. We know that foreign DNA can enter bacteria, and we can expect that such DNA will occasionally be integrated into the host chromosome. Recently Chang and Cohen have demonstrated that such integration of mammalian DNA occurs in E. coli cells, and at the same sites at which the in vitro experiments would cause their integration. This is hardly surprising, since the bacteria contain precisely the same enzymes that are used in the work in vitro. It now seems virtually impossible to doubt that mammalian DNA has been entering bacteria - - to be sure, at a low level of efficiency, but on such a scale in nature that the events must be quite frequent.

3) The spread of DNA in the microbial world, by several known mechanisms of genetic exchange, has been underestimated. It is increasingly apparent that plasmids and restriction enzymes have a major evolutionary role in the production in nature of hybrid organisms, with no sharp species boundaries between various bacterial strains.

4) The most serious source of misunderstanding was the failure to recognize the relevance of epidemiological principles for a problem that is fundamentally one in epidemiology and not in molecular biology. It is true that for precise quantitation of the hazards of specific novel organisms we would need data on those organisms. However, for a general assessment of the hazards knowledge of the class of organisms is sufficient. E. coli plus 0.1% foreign DNA will still be E. coli in its habitat and in its mechanism of spread. Hence knowledge of the mechanism of spread of E. coli and related enteric pathogens, and knowledge of the control of that spread by sanitation, is thoroughly pertinent. Even though

experts in epidemiology and infectious disease were not brought into the discussion on any substantial scale until very late, it is important to note their agreement, at the Falmouth Conference, that laboratory work with recombinants in E. coli K12 does not pose a public health hazard that requires extreme precautions, or that exceeds the familiar hazards of work with known pathogens.

5) Finally, the scientists who originally proposed a moratorium clearly underestimated the anxiety and confusion that would be generated by public discussion of conjectural hazards. These hazards were recognized as conjectural by those who raised the question, but they inevitably seemed real to others. An example of the resulting confusion between ideas and reality is provided by a statement in a news article that appeared in the December 1977 issue of Trends in Biochemical Sciences (and in a very similar form in Science magazine a month earlier). In a discussion of the reported use of an uncertified vector, in experiments on the cloning of the insulin gene, the reporter stated that "the earlier experiment clearly presented no threat to public health, since it was conducted in a medium security (P3) laboratory as required, and the vector has since been certified." I submit that it is nonsense to suggest that certification determines the real safety or danger of an experiment: what it determines is legality, based on presumptions about safety. The distinction is particularly important here because the regulations involving P1 to P4 and EK1 to EK3 have weak foundations, compared with the universally respected regulations that are based on the demonstrated biological effects of exposure to various levels of radioactivity.

I therefore conclude that it would be scientifically justifiable, though

perhaps politically not feasible, to introduce even greater relaxation of the guidelines than that recommended. In addition, I would like to recommend the following minor changes.

1) It seems to me important for the proposed guidelines to avoid meticulously any language that implies the reality of what are still entirely conjectural hazards. For example, in the middle column of page 409597 of the Federal register it is stated that "special laboratory design is used primarily in facilities in which experiments of moderate to high potential hazards are performed." The appropriate language would be something like "experiments thought to have moderate to high potential hazards." Any carelessness of phraseology in this connection helps perpetuate public misconceptions about the reality of the hazards.

2) The introduction should be strengthened, in order to present a more detailed justification for the proposed relaxations. The additional material might include the question of the novelty of the recombinants, the experimental demonstration of the integration of foreign DNA in bacteria, the data of Roy Curtiss on the negligible probability of escape of a plasmid from an EK2 strain, and the consensus reached by experts in enteric infections at Falmouth.

3) I would recommend a replacement for the statement, in column 1 of page 409597, that "the revised guidelines continue to be deliberately restrictive, with the intent of erring on the side of caution." While I appreciate the intent of the statement, it makes me uncomfortable to see a scientific group deliberately introducing error. Perhaps one could say something like the following: "Because of persistence of widespread public anxiety, which arose before these principles

and these findings were considered, the revised guidelines represent only a modest relaxation of the restrictions."

A final comment: medical research has always involved risk. If the present demands for freedom from risk had governed research in infectious disease in the past I doubt that we would have vaccines today.

Environmental Defense Fund

1525 18th Street, NW, Washington, D.C. 20036 • 202/833-1484

January 3, 1978

Donald Fredrickson, M.D.
Director
National Institutes of Health
Building One
Bethesda, MD 20014

Dear Dr. Fredrickson:

I enjoyed the opportunity to testify before the Advisory Committee and feel we have made some progress in addressing the failures of the proposed revised guidelines.

I cannot stress enough the need to realize that problems of procedure, access and credibility are central to the discussion of NIH regulation of recombinant DNA research and product development. The public rightfully perceives that regulation is a public policy decision to be made by representatives of the public interest and not a scientific decision to be made by representatives of special interests. Only when policy makers, in this case NIH through the recombinant DNA advisory committee, are free of real or perceived conflicts of interests will their decisions be accepted by the public. In the long run, bringing the public into the decision making process will strengthen the public's trust in science and insure science's continued support. Similarly, if protection of the public health or safety demands regulation or "guidelines", these regulations must be constructed in such a way as to enable enforcement. The roles and responsibilities section of the guidelines and the administrative procedures for its implementation do not insure compliance.

Many of the specific points that I think need attention were described in my testimony, which I imagine will be available for your inspection in transcript form. I would just like to briefly mention a few of them here:

1. The need for a detailed criteria document to serve as factual basis for the experimental guidelines section of the guidelines. As presently written, neither the guidelines nor the accompanying background booklets give adequate rationale for the containment requirements for each particular experiment.

2. Citizen membership on the DNA Advisory Committee. The setting of acceptable risk levels should not be entrusted to a

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committee representing only academic and primarily scientific interests. The committee membership must be broadened to include representatives of the public interest, including labor and environmental groups, elected or appointed governmental officials, and the non-scientific professions. Ideally the committee should be composed of a majority of non-scientists, with the scientific minority made up of people with experience in the disciplines relevant to setting biological and physical containment requirements and no financial ties to recombinant DNA research. A broad based committee will greatly enhance public confidence in NIH recombinant DNA policy. The need for a broad committee is further strengthened by the blatantly societal nature of decisions to allow deliberate release into the environment of recombinant organisms and industry involvement in recombinant DNA activities.

3. Beefed up enforcement procedures.

a. Mandatory worker and citizen representation on biohazard committees, to make it easier for individuals to report alleged violations.

b. Mandatory periodic inspections by biohazard committees of all ongoing projects. Copies of the inspection reports should be forwarded to NIH.

c. Open biohazard committee meetings.

d. Mid-level penalties for violations of the guidelines. It is obvious that a person's grant will not be cut off because of a single violation of the laboratory practices requirements. But some incentive is needed to deter these violations. The monetary penalties in the Cambridge DNA regulations may serve as a guide. Of course, the authority of NIH to levy such fines must be investigated. In addition, penalties should also be applicable to biohazard committee members who do not report violations to NIH.

e. Increased NIH staff.

4. Revision of the guidelines into language appropriate for regulations. The present guidelines are so vague as to make them unenforceable. Obviously written by people with little or no experience in regulation, they need to be completely rewritten to eliminate vagueness and loopholes. Moreover, required training and laboratory techniques must be specified. I urge you to study

the standards and criteria documents put out by other regulatory agencies. The OSHA standards for toxic substances mandate in detail required work practices, training and medical follow-up.

5. Inclusion of all hazardous recombinant DNA research under the guidelines. Any recombinant DNA activity that poses a risk to health or the environment should be covered by the guidelines regardless of whether the organism created is a novel one. S.1217 recognized this principle by mandating that only safe non-novel organisms were excluded from the guidelines. The aim of the guidelines is to protect public health and the environment from the hazards, not the novelty, of biological research.

6. Procedures for considering requests for exceptions to prohibited experiments must be delineated. The guidelines contain no criteria on which these decisions will be made. Moreover, there is no provision for publication of requests in the Federal Register and subsequent public comment. Procedures for public disclosure and comment on requests for new host-vector systems must also be worked out.

7. Extension of the guidelines to all recombinant DNA work at a facility receiving federal funds.

I urge you not to finalize revisions of the guidelines until the substantial modifications outlined herein and by other witnesses at the meeting are completed. I would be happy to discuss these matters further with members of your staff.

Sincerely,

Leslie Dach

Leslie Dach
Science Associate

LD/jkr

THE UNIVERSITY OF NEBRASKA-LINCOLN
LINCOLN, NEBRASKA 68583

Institute of Agriculture
and Natural Resources

Reply to:
Department of Plant Pathology
304 Plant Industry Building
East Campus
(402) 472-2858

January 3, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Department of Health, Education & Welfare
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This letter is in elaboration of my comments at the Dec. 15-16 meeting of the Advisory Committee to the Director, NIH.

1. The proposed revision on Recombinant DNA Research still retains the phrase "The capacity to infect some host cell" (p.49596) in the definition of recombinant DNA molecules. The term "infect" is not normally applied to agents, such as plasmids, requiring the specialized treatment used in recombinant DNA experiments for entry into host cells. The term is apt to be misleading to the public who may equate recombinant DNA molecules with pathogens which infect, (i.e. invade) and cause disease in their host. I therefore support the substitute definition proposed by Paul Berg (letter of December 5, 1977, document 31) in which recombinant DNA molecules are defined as "molecules which have been constructed outside of living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate [in] or be integrated into the genome of a living cell".

2. Affirming the testimony of Dr. Chilton, and the letters of Drs. Day (document 28) and Kado et al. (Dec. 5, 1977), I support deletion of the words "and plant pathogens" (p. 49602). P2 + EK2 or P3 + EK1 conditions are sufficient for most allowable plant pathogens. In fact, P1 + EK2 or P2 + EK1 conditions are undoubtedly sufficient for most allowable experiments.

   As indicated by many investigators, the crown gall bacterium Agrobacterium tumefaciens offers the most promise for introducing foreign DNA into plants. Yet there is concern (Albersheim, document 1; Simring, Dec. 15 remarks) that this bacterium poses hazard to agriculture. It would be ironic to further restrict, by P3 - EK2 conditions, for example, experiments with A. tumefaciens since work on the genetics of this bacterium and its plasmids is progressing more rapidly than for any other bacterial plant pathogen. This work includes analysis of the genes determining pathogenicity. The possibility thus exists for excision of pathogenicity determinants without loss of those determinants for entry

and maintenance in plants. Furthermore, A. tumefaciens is the only phytopathogenic bacterium that can be adequately controlled both by chemical (non-antibiotic) means and, more significantly, by biological means. Biological control by certain A. radiobacter strains has proved economically effective on a variety of crops, both in this country and abroad.

3. The letter by Kado et al. (Dec. 5, 1977) suggesting a classification of plant pathogenic bacteria akin to the CDC classification is an admirable first step in such a classification. It should serve as a point of departure for further discussion, (there are several areas of potential disagreement), and such a document should include viruses, fungi, and potential transcripts of viroids.

4. Of the potential for agriculture of recombinant DNA technology is to be realized, alternate host-vector systems should be encouraged. It is unlikely that agriculture would best be served through the use of E. coli (or B. subtilis).

5. Risk assessment experiments with plant pathogens should be considered under the proposed exemption clause. Pathogens of low virulence or pathogens of non-economic crops might serve as models for such experiments. U.S.D.A. support should be sought for such a task.

6. Although premature, consideration should be given to the mechanism for eventual release of plant material altered by means of in vitro recombinant DNA, into the environment. As others have pointed out previously, if benefits are to be realized in agriculture, plant material must be propagated outside the laboratory.

7. The most immediate benefits from recombinant DNA to industry seem to be in antibiotic amplification, rare drug production, and certain hormones. If these are to be produced at affordable cost to consumers, industrial and proprietary rights must be considered. Along these lines, I believe the specific advice of a patent attorney would be of value to NIH, before final revision of the proposed guidelines.

Finally, I appreciate your concern that the guidelines are deficient in treatment of plants (and insects) and their associated microorganisms. However, I believe we presently lack the data base to consider more detailed benefits and risks beyond those already covered in the revised guidelines.

In summary, with the exception of minor points, the revised guidelines appear satisfactory for the plant sciences.

Sincerely yours,

Anne K. Vidaver
Associate Professor

xc: Peter Day
John Fulkerson
Milton Zaitlin
Clarence Kado
Arthur Kelman
Charles McCarthy
Waclaw Szybalski

GEORGETOWN UNIVERSITY LAW CENTER
WASHINGTON, D. C. 20001

PATRICIA KING
ASSOCIATE PROFESSOR OF LAW

January 4, 1978

Dr. Donald Frederickson
Director, National Institutes of Health
Department of Health, Education and Welfare
Bethesda, Maryland 20014

Dear Dr. Frederickson:

At your request I am putting in writing my comments concerning the proposed guidelines on recominant DNA research. At the outset let me say that the NIH is to be congratulated for doing such a fine job in handling the recombinant DNA issue. Your efforts have certainly helped to allay fears and concerns about pursuing this line of scientific inquiry.

However, if the public and the scientific community are to continue to have faith in NIH policy with respect to recombinant DNA research, your policies and processes must be improved. They must be improved, because it appears to me that confidence in the approach adopted by NIH is largely dependent upon the credibility of the process that produces the guidelines and revisions. As you are aware, I was particularly concerned with the process by which these particular revisions were generated. With these general remarks as background, I offer the following more specific comments:

1. The NIH should utilize whatever authority it presently has, or request the Congress to grant it such authority, to extend the coverage of the guidelines to non-government conducted or sponsored research.

2. The roles and responsibilities of the NIH committees involved in the decision-making process need re-evaluation.

The structure and operation of the DNA Molecule Program Advisory Committee should be re-examined. Consideration should be given to changing its composition (I understand it has only two "public" members), and its method of operation. I believe that the committee should operate openly, hold public hearings and insure that the data forming the basis of its conclusions is available to the public. It should in any case have its method of operation publicly announced, and be immune from concern about the "political" wisdom of its conclusions.

The role of the Director's Advisory Committee should also be reviewed. Although this committee may have many useful purposes, its current structure and format are not sufficient in themselves to inspire public confidence. Its members (at least some of them) cannot give informed and credible advice based upon a day and a half of hearings and reports.

3. The NIH in guidelines, supplementary issuances or programs should promote or take the lead in standardizing such things as training of laboratory workers, equipment design, safety procedures, test procedures, operations of biohazard committees, etc.

4. The procedure for determining whether a procedure is novel vs. non-novel should be spelled out since it is my understanding that it is impossible at present to furnish researchers with a list of such experiments.

5. P_1K_1 research can be exempted from coverage.

I am pleased to have had the opportunity to meet you, and I enjoyed serving on the Advisory Committee.

Sincerely yours,

Patricia King

Patricia A. King

PAK:mb
cc: Waclaw Szybalski

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January 4, 1978

Dr. Donald Fredrickson
Office of the Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

The meeting on the proposed Revisions to the NIH Guidelines was conducted with your customary aplomb and efficiency. I felt that it provided a good opportunity for the expression and examination of a variety of points of view.

I enclose my comments on the proposed revisions.

With best regards,

Bob

Robert L. Sinsheimer
Chancellor

Enclosure

ES/NIH Distr., 1/10/78: PERPICH
Info cy: Fredrickson,Stetten,Talbot,Gartland,Curtin
ES/NIH has orig. for Carrigan

COMMENTS CONCERNING PROPOSED REVISIONS TO THE NIH
GUIDELINES FOR RECOMBINANT DNA RESEARCH

While this conference was called to examine the proposed revisions to the NIH guidelines, these cannot be considered without some reference to the initial existent guidelines.

From my point of view, the guidelines are informed by a perspective which is:

1) Extraordinarily anthropocentric. The whole framework of containment provisions exhibits a dominant bias toward the specific protection of human beings. The containment requirements parallel presumed phylogenetic relationships to man. Provisions for containment of viral nucleic acids (or components) reflect the ability of such viruses to grow in primate or human cells.

The necessity for the protection of other species is given much less weight, if any. Such a view is, at best, a short-sighted anthropocentrism. The importance of plants was frequently mentioned at this meeting. Similarly many, many other life forms--microbes, nematodes, insects, etc., play vital ecological roles. We should be concerned with their safety as well.

Even with respect to man, the guidelines reflect the experience and capabilities of disease containment in more advanced countries with excellent sanitation and medical facilities. They seem much less reflective of the disease potentials in the less advanced societies which include most of humanity. With modern transportation one can hardly be confident of restricting the spread of any microbial strains.

2) Extraordinarily confident of the completeness of our knowledge of microorganisms and of our ability to predict the consequences of changes of scale of 10^{10} or greater. The complexity of biological organisms seldom provides the unexceptionable generalizations found in physics or chemistry.

3) Dangerously narrow in their preoccupation with recombinant DNA to the exclusion of other forms of genetic research capable of producing recombinant cells and organisms of unknown potentials, i.e., cell fusion, chromosomal transfer.

Such a perspective continues to be manifest in the proposed revisions. It may indeed represent the political "center" but it does not to my mind reflect the objectivity with which we are familiar in everyday science.

To turn to the "Revisions." There appear to be two general classes: 1) Those which represent "tidying up" the language or details of the existent Guidelines, e.g. improving the definition of recombinant DNA, introducing the HV nomenclature, etc. With most of these I have no quarrel. I do suggest that the proposed revised and expanded classification of research with viral or sub-viral genomes has not been thoroughly thought through and needs more analysis. 2) Those which represent a downgrading of the required containment provisions, based principally upon the "new" information as to the properties of E. Coli K12.

With these I cannot at this time agree. In the first place the "new" information is not, in large part, available to me nor to the scientific community where it can

be properly scrutinized. I do not think it reasonable to make public policy based upon as yet private communications.

Further, the burden of the new information, as I understand it, is that E. Coli is a "poor" pathogen, that E. Coli K12 is an enfeebled strain as a consequence of its long years of laboratory passage and that it has so far proven impossible to convert K12 to pathogenicity. Even if accepted as correct, the significance of such observations may be questioned.

Because E. Coli is a "poor" pathogen does not mean that it might not be convertible to a "good" pathogen by the increment of one or a few genes. Most pathogenic organisms reach an equilibrium level of pathogenicity with respect to their common hosts, lest all hosts be killed off. Considering the ubiquitous presence of E. Coli in man, it would be expected that current strains will not be highly pathogenic--but that does not prove they lack the potential.

The enfeebled nature of K12 is presumably the consequence of mutation(s) introduced during its laboratory passage. This thought gives rise to the suspicion that different strains of K12 (and there any many in use) having different histories may not all be similarly enfeebled. Has this been studied?

The failure to convert K12 to to pathogenicity through the introduction of certain plasmids or Salmonella genes is comforting but not definitive. As long as the detailed nature of the mutations on K12 which prevent the expression of pathogenicity is unknown, we cannot know how difficult the introduction of pathogenicity would be by the appropriate route. Most of the factors affecting pathogenicity act by modification of the cell surface. Some relatively simple (and thus potentially reversible) modification of a cell surface component in K12 could be sufficient to block the introduction of pathogenicity by any of the means thus far attempted.

The potential for transfer of the recombinant plasmids from K12 to other bacterial species has only been studied under a limited variety of circumstances. The potential for such transfer in the wide variety of natural environments in which Coli is found has not been explored.

Even were the statements about the reduced hazard now perceived to be associated with E. Coli K12 recombinant DNA experiments to be accepted at full value, there is still no way to assess the absolute risk associated with these experiments. It may be less than it was thought to be--but the whole structure of graded risk implicit in the guidelines floats at some level dependent upon investigatorial confidence rather than documented fact. If such experiments are "less risky," because of the "float" those who regarded the Guidelines with derision may now regard them with greater derision while those who felt they were inadequate in the first place may still find them to be inadequate.

At this point I would like to issue a strong caution concerning the introduction of new HV systems for recombinant DNA work. If, as I believe, so much uncertainty continues to surround research with so well-studied an organism as E. Coli, our ignorance with regard to any other vector, its ecological involvements, the organisms with which it can exchange DNA, etc., etc. must be that much greater. I point out again in this regard our need to be concerned with the safety of other life forms as well as man.

I believe it is also important to keep in mind that reductions, particularly in physical containment as from P3 to P2 will significantly increase the number of sites where

research of the type concerned is carried out and correspondingly the number of people involved.

On a more positive note I would like specifically to endorse the provision within the revised Guidelines for discretion by the Director of NIH to permit relaxation of containment requirements for specific purposes. I would hope that this discretion would be used principally to allow the performance of risk assessment experiments--and particularly not be used merely to allow the performance in this country of experiments that may be performed in (misguided?) foreign lands.

I would also favor the elimination, from the Guidelines, of regulation of those experiments which are simply laboratory duplications of those recombinations occurring frequently in Nature. (In this regard I do not consider the "new" evidence regarding the possible formation of inter-species recombinants in Nature as a serious argument against the "novelty" of recombinant DNA research. It is not meaningful to compare the possible production of a chimeric organism, at some wholly unknown frequency in Nature with the deliberate synthesis and growth of 10^{10} - 10^{12} chimeric organisms in a single experiment. The argument can be further reduced to absurdity by pointing out that it is now readily feasible to make combinations of DNAs wholly improbable ever to come together in Nature.)

I would also favor the exclusion of all P1 EK1 experiments from the guidelines, etc. as I do not believe this category provides a meaningful degree of containment.

As a last point I believe it is very important to institute a routine program to monitor and report upon the health status of all personnel engaged in research with recombinant DNA, tumor viruses, pathogenic organisms, etc. It is simply meaningless to state (as is done) that "no one has ever been made ill by recombinant DNA research," when there is no baseline against which such illness (unless of near epidemic proportion) would be detected. (It should also be borne in mind that a significant lag period can be involved--as was the case with radiologists--before an occupational hazard may be detected.)

As always, I empathize with the difficulty of your decisions.

Robert L. Sinsheimer

THE UNIVERSITY AT ALBANY

January 4, 1978

Dr. Donald Fredrickson, Director
National Institutes of Health
Department of Health, Education
and Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing to express my opposition to the proposed revisions (9/27/77) of the NIH Guidelines for Research Involving Recombinant DNA Molecules. As a developmental biologist specializing in gene control in vertebrate systems, I am concerned that very little attention has been paid, both in the original Guidelines and in the proposed revisions, to current ideas (and ignorance) of the origins of pathogenicity. It seems to me that none of the evidence presented in the Background document (November 1977) compiled by your office in support of relaxing the Guidelines speaks to points raised by Dr. Robert Sinsheimer and others in criticism of the 1976 document.

To illustrate my concerns, I would like to juxtapose some passages in the Background document with some passages from a recent article in "The New Yorker" magazine (January 2, 1978) on Dr. Lewis Thomas, president of the Memorial Sloan-Kettering Cancer Center, a specialist on the interaction of bacteria with higher organisms. Though Dr. Thomas himself minimizes the hazards of recombinant DNA research, several of the points he raises suggest a more cautious approach is in order.

> ....E. coli K-12 is so severely enfeebled in many of the properties that are necessary for survival in nature and for pathogenicity that it is incapable of being inadvertently converted into an epidemic pathogen by the insertion of DNA by recombinant techniques. (Background...p. 32.)
> ....E. coli K-12 will colonize the artificial intestinal environment of germ-free mice. (Background...p. 30.)

DEPARTMENT OF BIOLOGICAL SCIENCES
STATE UNIVERSITY OF NEW YORK AT ALBANY • 1400 WASHINGTON AVENUE • ALBANY, NEW YORK 12222

"The diptheria toxin is a chemical so closely related to a component of our own cells involved in protein synthesis that it's mistaken for that by the cell and locks onto a part of the apparatus for making proteins and shuts the process off. But in order to make that toxin the diptheria bacillus itself has to have been infected by a virus. A perfectly healthy diptheria bacillus is innocuous. It's not until it has been invaded by a phage...and has incorporated the genetic content of the phage into its own genetic content that it has the information for making diptheria toxin. There has been speculation that the information that comes in by way of the phage may itself have come long ago from eukaryotic cells...To a degree, therefore, it looks as though some infectious diseases were really accidents--biological accidents." (Dr. Thomas, in "The New Yorker", p. 40.)

Containment criteria for an organism producing a toxic product has been clarified...many toxins are the end-products of a complex set of biochemical reactions...In these cases, the danger of inadvertantly cloning the toxin-producing mechanism into E. coli is virtually nil. Therefore, if proof exists that a toxin is of this category, the containment may reasonably be lowered to that of a related organism that does not produce a toxin. (Background... p. 36.)

"...rheumatic fever is an after affect of a specific streptococcus..."There is something bizarre about the illness...When rheumatic fever develops, it does not do so for ten days or two weeks after the first infection... by which time the original throat infection has already disappeared...The disease has some similarities to a generalized allergic reaction...It is as though the streptococcus infection had turned on some kind of highly inappropriate immunological reaction, in which the host's own defense mechanisms have brought about damage to his organs--in this case the heart." (Dr. Thomas, in "The New Yorker", p. 36.)

"Most of the gram-negative organisms possess at their surfaces endotoxins that are incorporated into the surface wall and are released when the organism dies. Nobody really knows how an endotoxin works, but what it does when it is injected into animals, or when we are exposed to it through an infection, is to cause a complex series of reactions, any one of which would be classed as an

> important part of illness-high fever, and when the dose is large enough shock develops, with the bottom dropping out of the blood pressure, followed by coma and death. There are peculiar kinds of hemorrhagic reactions that occur in the skin and in a lot of internal organs, and it looks as though a lot of important physiological mechanisms had been unhinged by this toxin. But when you look at an endotoxin closely it's difficult to find anything about it that is really toxic in the sense that it inflicts a primary kind of damage. It doesn't poison the cells if you put it in cell cultures. It looks more like a signal than like a toxin. (Dr. Thomas, in "The New Yorker", p. 40; emphases added.)

I think that it must be admitted that the subtleties of why an innocuous organism becomes pathogenic under certain conditions are not well understood. When the possibilities are considered of bacteria causing misreading of eukaryotic control signals, and autoimmune reactions, after having incorporated fragments of eukaryotic genomes, it can be seen that the definition of "toxin" under the present Guidelines and the proposed revisions are inadequate. Given Dr. Thomas' examples it is apparent that virtually any highly conserved, physiologically active eukaryotic protein (collagen, histones, initiation factors) or fragment thereof could be highly toxic when introduced out of context by a bacterium which received the appropriate gene in a recombination experiment, or picked it up from another which did so.

I therefore do not understand the confidence of those who claim that novel pathogens cannot be created in recombinant DNA experiments. I think that if the experiments are to proceed at all, we are entirely dependent on high containment to avoid populating the biosphere with a whole slew of critically modified microorganisms some of which will eventually cause grave difficulties to existing metazoans. While EK2-P4 conditions conceivably meet these safety requirements, most work is now going on at much lower levels of containment. Given the probabilities of human error and inevitable occasional contamination of bacterial host stocks under these conditions, it would seem that the present Guidelines should be strengthened rather than relaxed.

I would appreciate your placing this letter in the public record as testimony regarding the proposed revisions.

Sincerely,

Stuart A Newman

Stuart A. Newman
Assistant Professor of
Biological Sciences

SAN:lms

4 January, 1978

Dr. Donald Frederickson
Director, National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Frederickson,

Enclosed you will find a copy of my written testimony for the Advisory Committee hearings of last December. I hope it will be helpful to you as you are making your final decisions about the new guidelines.

You and your staff should feel quite satisfied for having conducted such educational and stimulating hearings. Even in spite of the marathon-like duration of the sessions, I think most people remained interested and became better informed right up to the end. I especially benefited from discussions with committee members and other witnesses both in the hearings themeselves and at breaks.

I am, of course, extremely grateful for your inviting me to participate in the hearings. They were a welcome opportunity for me to represent the Sierra Club in this important issue and to present my views. In addition, it was encouraging to see that public or non-science oriented input into science-policy discussions can be successful and beneficial to both the parties involved and the policy questions themselves. I hope you will continue and even make more frequent such discussions in the future.

Again, many thanks.

Sincerely,

Nancy Pfund

Nancy Pfund

TESTIMONY BEFORE THE NIH DIRECTOR'S ADVISORY COMMITTEE
on
DRAFT REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH
by
NANCY PFUND
SIERRA CLUB LOBBYIST
1531 El Camino Real
Palo Alto, California 94301
(or contact Washington office, 330 Pennslyvania Ave. SE 20003)

15 December, 1977

I. Introduction

Thank you for giving me the opportunity to testify. I hope public hearings like these can be continued on a regular basis since they lend legitimacy to the decisionmaking process in this very important area.

While I hope today's discussions will be insightful and worthwhile, I must express my disappointment at the timing and purpose of these hearings.

That is, they represent too little effort, too late in the game.

The draft guidelines have already been revised downward. Why?

The introduction states that the Advisory Committee based its revisions on new data which diminuish the estimate of risk associated with recombinant DNA research in E. Coli K-12 systems.

What are these data? Where are they published? Why have they not been widely circulated and subjected to comprehensive review by experts and the public alike? These data are not referenced in the guidelines and the references in the background document include unpublished articles, informal reports, letters and other information which have not been submitted to traditional means of scientific review nor to public debate.

The fact that the NIH Advisory Committee gained access to new information and used it in developing the new guidelines without securing outside comment while decisions were being made makes a mockery of public participation in this process. As a result, many of the changes seem baffling and arbitrary even to those of us who are following this issue. If the NIH is committed to getting public input it must equip the public with the data its own Advisory Committee uses to justify its decisions.

I find it ironic that while the NIH demands rigor in establishing proof from experimental data from its grantees, it settles for less in its own operation. And while intelligent evaluation of new information may have characterized the meetings of the Advisory Committee, by presenting the guidelines as a fait accompli with no indications of the reasoning behind the revisions, the NIH is undermining the principles of informed democratic decisionmaking.

Essentially, we have no inkling as to how the committee reached its decisions.

I quote one example from the background (page 10):

> There are catagories of experiments for which the

containment levels are specifically mandated in the 1976 Guidelines but for which some discretion is permitted in the proposed revision.

The logic and justification for such discretions should be matters for discussion by a wide range of individuals, and not confined to an Advisory Committee whose composition and scope are not representative of the various positions and perspectives on this issue.

One of the changes without ample justification appears in the intoduction and concerns the defintion of recombinant DNA. While it may be reasonable to exclude certain recombinants which are both "not novel" and deemed non-hazardous, the focus must always be on ensuring safety, not proving or protecting non-novelty.

In addition, the last recommendation in the Introduction, where it is urged that all publicaitons dealing with recombinant DNA work include a description of the physical and biological containment procedures, should be made mandatory in order to convey the absolute importance of adheringto these guidelines.

II. Physical Containment

1. The principle of physical containment, especially as it is reflected in the upper 'P' levels in the guidelines, is a valid measure to take to minimize risk. However, all of the various matrices designed to create escape-proof situations may go for naught if a similarly detailed approach to shipping of recombinant DNA organisms is not developed. At present, the gradations for shipping requirements relate to the volume of the material sent, not to its level of potential hazard. This approach seems inconsistent with the philosophy of physical containment and does not adequately address the problems of ensuring safety when the state of the research will be characterized by extensive use and wide-scale productions of recombinant DNA organisms. The new requirement for use of registered mail for shipping, while an improvement, does not answer these concerns and is based on a perhaps unwarranted confidence in the reliability of the postal system.

2. The emphasis on development of good working practices and training in aseptic techniques in section A is a welcome addition. To ensure that such procedures do, in fact, develop, I would recommend that the 'shoulds' be changed to 'shalls' (regarding establishing training, emergency plans and immunization of workers). In addition, a grievance procedure could be established to help those who feel that training and/or lab practices are inadequate to protect health and safety.

III. Biological Containment

Certification of Host-Vector Systems

Certification of Host-Vector systems must be undertaken with deliberate caution due to the many unknown factors inherent in a new host or vector. We can learn from our experience with E.Coli, a system about which we know a great deal, that many experiments and tests must be done before any claims about safety can be legitamately made. In the guidelines, the criteria developed for approving new host-vector systems are too vague and lack sufficient inputfrom relevant disciplines such as epidemiology or microbial ecology. More importantly, the process by which H-V systems are approved may act to weaken these standards. The NIH creates a dangerous precedent by mandating initial review of HV systems to a subcommitte of an already too narrowly focussed Advisory Committee. While this subcommittee may be strengthened by the inclusion of special members capable of evaluating the sufficiency of the data and assessing the impact of widescale use of the system, it may just as well be weakened by its vulnerability to 'experts' who may have a strong interest in using the HV system they are supposed to review.

By relying on vaguely constituted subcommittees, the NIH skirts the important issues of who should determine what will be sufficient data to merit certification and on what grounds such decisions should be made. The NIH should make an aggressive effort to disseminate all such information to the public and relevant professionals before any decisions are made. One way to do this would be to require, not merely encourage as the guidelines now state, investigators to publish their data on these systems. By circulating the data and by making it explicit in the guidelines that these comments will be evaluated by a diversely composed group representative of the various interest involved, a more responsive and responsible policymaking process will ensue.

IV. Experimental Guidelines

Exemptions

Creating exemptions to the prohibited production of large-scale experiments or the deliberate release of any recombinant DNA organism into the environment places the very raison d'être of these guidelines in je pardy. If exceptions are made to the 10 liter limit, for example, what happens to the efficacy of cont nment? Will adjustments have to be made? Where are the provisions and standards for such adjustment in these guidelines?

While exemptions may be necessary in order to pursue risk-assessment studies, exemptions to private industry raise a myriad of difficult questions. However, requests for exemption may well come from private industry, as it has already expressed interest in changing the 10 liter

limit requirement. Thus, in granting exemptions, the Advisory Committee would be going far beyond the individual cases in question to pave the way toward industrial exploitation of the as yet immature recombinant technology. This is a critical area which requires much study and discussion because of the magnitude and scope of its societal and environmental implications. The Advisory Committee mechanism, as it is presently operated, is ill-equipped to make these broader decisions. Due to its dominantion by academic researchers, it may even be unprepared to ask all of the right questions. One of the more obvious weaknesses in terms of its composition is the omission of any representatives from relevant labor unions. (see section on Roles and Responsibilities)

One way to avoid the problems of industrial exploitation of the recombinant technology in its early stages would be to declare, at least temporarily, recombinant DNA organisms to be national resources and continue efforts to develop a repository for them. Such a policy would ensure that everyone could obtain these organisms for study, including representatives from private industry, if proper licensing procedures were developed as well. This procedure has been advocated by Dr. Marc Lappé, Chief of the Office of Health, Law and Values in the California Department of Health. His comments can be found on pages 32-34 of the Comments booklet.

Containment Levels for E. Coli hosts

One assumption in devising containment levels whose factual basis is unclear has been carried over from the 1976 Guidelines. That is that the potential risk is somehow inversely proportional to the phylogenetic distance from humans of the source of cloned DNA. This is apparently based upon the notion that the more closely related the cloned DNA is to humans, the greater the chance of gene expression in humans. What is the reasoning behind this? Why is bird DNA somehow safer than squirrel DNA?

(1) The expression of genes in a way that poses a hazard may not necessarily be in humans, but in bacteria which are infectious, or in plants or other organisms which pose a threat other than human infection.
(2) What about genetic modifications that do not involve structural genes, but rather control signals? Is there any justification for a phylogenetic effect?
(3) If the expression of foreign proteins in humans poses an immunological risk, then the risk may be greater, the more foreign the DNA is.
(4) Humans are not the sole occupants of this planet.

The Lowering of Containment Levels by Local Biohazards Committees

The principle of lowering containments for characterized or purefied DNA preparations may or may not be sound; it is difficult to judge since we do not what went into making this decision. At

any rate, I feel that it is a mistake to leave the responsibility for lowering containment to the Institutional Biohazards Committee without strengthening the structure and functioning of this committee. Too often, these committees fail to critically investigate either the data or the working habits of the investigator in question. Because diversity of representation on these committees is not required, decisions may be made without paying sufficient attention to the quality or scope of the information submitted.

For these reasons, I find this provision inadequate. The problems with it could be resolved by strengthening the Institutional Biohazards Committee and especially by strengthening the enforcement provisions and procedures.

V. Roles and Responsibilities

The guidelines as they are now written confer a large amount of responsibility for enforcement to the principal investigator and the institution. As the UCSF experience indicates, this is an unrealistic and unacceptable approach to enforcement. Procedures must be developed to monitor the Institutional Biohazards Committees as well as the Principal Investigators. One way to do this is to establish better communication between the IBCs and local citizens. Specifically, this could be achieved by requiring rather than recommending that IBCs include persons representing the areas of standards of practice, community attitudes, health and environmental concerns. In addition, the IBC should be required to have adequate representation from workers and non-institutionally affiliated persons.

Another way to increase the accountability of both the IBC and the labs doing recombinant DNA research would be to require that the majority, if not all of the meetings of the IBC be open to the public. Mere minutes of these meetings are not sufficient to inform the public and institutional employees of the extent and nature of local recombinant DNA research. By having open meetings, the public will be better informed and better able to contribute to decisions and actions aimed at ensuring safety and upholding the guidelines.

As far as monitoring of Principal Investigators is concerned, if no legislation is forthcoming setting up a regulatory process for this research, the NIH staff should be fortified so that it can tackle the responsibility of enforcement. Relying on outside sources for information on violations of the guidelines indicates a gap in the enforcement process. The guidelines must be made more specific so that each level of regulation feeds into the next. Provisions and funds should be made both to establish criteria for monitoring and to develop a process for their implementation. This could include unannounced bimonthly monitoring of labs by either biohazards-committee members, a biological safety officer, or any other individual who could show that he or she could effectively investigate the labs following

established procedures. Monitoring reports should be filed regularly with the NIH. Provisions should be made to pay local monitors. The NIH could in turn establish postions to provide for periodic monitoring of labs by its own staff.

The feasability of having the NIH establish fining provisions for those who violate the guidelines should be explored. This would bring flexability to enforcement of the guidelines, as the amount of the fine would be proportional to the nature of the violation. Fining provisions would have the additional advantage of creating an obvious incentive to uphold the Guidelines.

Role of the Advisory Committee

The lack of adequate diversity in composition which plagues the Institutional Biohazards Committee can also be found in the Advisory Committee. With all due respect to its members, the Committee has an artificially narrow approach to its task and a lack of accountability to the public in the crucial stages of decisionmaking. Dr. Suzuki's testimony outlines many areas of concern which have not been addressed by this committee, including the issue of human genetic engineering.

If the Advisory Committee is to become more responsive to social, ethicaland environmental concerns it must expand or divide. That is, either the present technically oriented committee should be changed to include more experts at evaluating the impacts of the recombinant technology, workers and members of the public, or a complementary committee should be formed to address these concerns. While technical expertise is indeed an essential component of a policy-making mechanism, it should not exist to the exclusion of comprehensive attention to other aspects of the issue.

The NIH should actively pursue a process for decisionmaking which does not spoon-feed to the public but is instead nourished by the public's input. Two ways to achieve this include improving the accessability of the committee and changing the selection process of its members. Perhaps the committee could follow the model of the National Commission for the Protection of Human Subjects and meet at various locations throughout the country. This would provide opportunity for local-level input. The committee could also have meetings with paid invited public witnesses on a regular basis. Minutes of these meetings (and all data used in the committee's deliberations) should be published and circulated. The selection of members for the Advisory Committee should be done with contributions (e.g., lists of names of potential members) from all of the various interests involved in this issue.

By developing procedures that open up the decisionmaking process for recombinant DNA research policy, the ultimate policy set orth becomes more justifiable. In addition, future essays in developing science policy will benefit from this process.

ROCHE INSTITUTE OF MOLECULAR BIOLOGY

NUTLEY, NEW JERSEY 07110

January 5, 1978

Dr. Donald S. Fredrickson
Office of the Director
National Institutes of Health
Bldg. 1 Room 124
Bethesda, Maryland 20014

Dear Don:

I regret not being able to attend the Director's Advisory Committee Meeting on December 15-16, 1977 concerning the "Proposed Revisions to the NIH Guidelines for Research on Recombinant DNA". I am informed, however, that your records will be kept open for an additional 30 days, and I am therefore taking this opportunity to offer my comments.

I understand from Dr. Ann Skalka's report to me concerning the meeting, from Nicholas Wade's report in Science (Jan. 6), and from following developments over the last several months that the modest changes suggested in the "Proposed Revisions" are certainly justified on scientific grounds. Despite suggestions made at the meeting on possible procedural changes which may be employed in future revisions, I urge you to adopt the present revisions as expeditiously as possible. The reasons are twofold:

First: The concept of continuous "updating" was an integral part of the original guidelines. Indeed, this process was, I believe, to take place annually. It appears that almost two full years will have passed before even the current modest revisions will take effect. Such delay is surely not in the best interest of science, or the credibility desired by the NIH in its leadership role in the area.

Second: As you know, several state and local governments (including the State of New Jersey) are currently developing their own legislation in this area. Similar Federal action may take place in this session of Congress. These laws will be based, for the most part, on the version of the Guidelines currently in effect. It is important that these laws include the most updated version possible.

Please feel free to call on me if you should need any help in your deliberations on this matter.

Sincerely yours,

Sidney Udenfriend, Ph.D.
Director

SU:sa

Meeting of the Director's Advisory Committee

NIH
Dec. 15-16, 1977

Presentation by David T. Suzuki

> "Dr. Faustus, Dr. Frankenstein, Dr. Moreau, Dr. Jekyll, Dr. Cyclops, Dr. Caligari, Dr. Strangelove. The scientist who does not face up to the warning in this persistent folklore of mad doctors is himself the worst enemy of science. In these images of our popular culture resides a legitimate public fear of the scientist's stripped down, depersonalized conception of knowledge -- a fear that our scientists, well-intentioned and decent men and women all, will go on being titans who create monsters."
> Theodore Roszak.

For the past twenty years, science has been the dominant element of my life, rewarding me with the surprise and joy of discovery beyond my wildest dreams. I care passionately about science as the highest form of intellectual activity in our culture. And it's in a longterm social context of science that I see the importance of the recombinant DNA issue. What has excited me about the public interest in recombinant DNA was the hope that scientists would have forced upon them an understanding of the extent of their social responsibility while the public in turn would have to become educated about the nature of the scientific enterprise. Neither, I'm afraid, has actually happened.

I have been a certified Drosophila geneticist for sixteen years and for the past seven, people in my laboratory have been involved in finding the chromosome locations of TRNA genes. Several laboratories using plasmids with Drosophila DNA will render our work obsolete within a year. So you can imagine the pressure within my group to "get in on the action" ourselves. Indeed, my colleague, Gordon Tener of the Biochemistry Dept. has received a special grant to build containment facilities in accordance to the guidelines of the Medical Research Council of Canada.

Nevertheless, I have pledged (Science Forum, 58:12 , 1977) not to allow any recombinant DNA work to be done in my laboratory. Nor will my grants or my name be cited on any papers reporting such work. I have decided on this action not because I fear accidental escape of a pathogenic creation because I am convinced there is little evidence to support such a scenario. (I must say though, that I am astounded at the confidence with which microbiologists feel they can predict the behavior of newly produced organisms. Surely it's the unexpected that we constantly find that make experiments worth doing. Furthermore, we ought to temper our confidence with the knowledge that time lags of up to a generation can occur between cause and effect as was the case with DES and vaginal cancer. Similarly, some agents have effects that are so subtle, statistically significant differences only emerge when millions of people are exposed as was shown by the relationship between birth control pills and heart problems).

I will not get involved with recombinant DNA because at my age, the doing of science has given me more than I ever expected. And I still derive enormous vicarious satisfaction with someone's elegant experiments. Thus, I can derive the excitement of recombinant DNA work while still lacking the vested interest in the technique that would prevent me from entering the discussions more objectively. For it is the longterm use to which DNA technology will be put that concerns me most and if I were directly involved with the work, my perspective would be too restricted to examine the broader social possibilities.

My reasons for this individual moratorium are very personal. I was born in Canada of Canadian parents in 1936. On Dec. 7, 1941, the Japanese attacked Pearl Harbor. In January, 1942, I was sent to a concentration camp for four years for committing the crime of having genes that came from Japan three generations ago. General DeWitt, the commander

in charge of the incarceration of Japanese-Americans, uttered his infamous remark:

> "A Jap's a Jap. It doesn't matter where they're born. They're sneaky and can't be trusted."

Now that is a statement about genetics, that deceit and treachery are racially inherited traits. Dewitt's belief didn't spring out of the blue -- it was fostered and encouraged by "scientific" claims made by some of the most eminent biologists and geneticists in the early part of this century. In their euphoria with the Darwinian theory of evolution by survival of the fittest and with the discovery of Mendel's laws of heredity providing a basis for natural selection, scientists rallied around the field of eugenics. Often extrapolating from fur color in guinea pigs and egg laying in chickens, many geneticists made sweeping pronouncements about the racial basis for intelligence, criminality and poverty. In the same way, Nazi Germany's elaborate program of racial purification and eugenics did not leap, full blown, from the brain of a single madman. It was made possible by the contribution and support of some of the finest minds in world science.

I don't want to belabor this, but a simple inspection of the history of science reveals that usually for the most lofty principles, for the best of intentions, the scientific community has contributed its expertise and technology for what would later be seen as misguided and ignorant purposes.

> "What becomes evident is that scientific leaders, when faced with a choice between the imperatives of conscience and power, nationalism and internationalism, justice and patriotism, invariably gravitated toward power, nationalism and patriotism."
>
> Joseph Haberer.

As the amount of scientific information has exploded, scientists, of necessity, have had to become specialists within specialties with the result that we know less about what's happening in other areas of science and we've lost all sense of a historical and cultural perspective of this

activity. In Canada, students begin to specialize in science in high school. In college they earn Bachelor of Science degrees without ever having to study literature, art, history, philosophy or religion. As well, by the time they're practising scientists, papers older than ten years are often regarded as "classics" (worth citing but not reading). In order to remain at the cutting edge of new knowledge, scientists must become tunnel visioned. We, as scientists are incapable of understanding what the real implications and applications of our work will be. We don't have the breadth, the time, the objectivity or the interest to find out.

> "Modern science has been singularly devoid of any serious concern with fundamental questions -- for example, those involving the relations between means and ends. Its overriding instrumentalism has been expressed in its desire to control and dominate nature, almost as an end unto itself." Joseph Haberer.

Yet to-day, the most powerful force affecting society is science when applied by technology. There is no place on this planet we can go without using the products or encountering the debris of science and technology. When I was a child, there were no such things as plastics, oral contraceptives, microcomputers, DDT, antibiotics, nuclear power, satellites, television, polio vaccine, tranquillizers, jet planes, heart and kidney transplants, transistors, lasers, xerox and amniocentesis. These have all become a part of our world during my lifetime. For my children, a world devoid of these inventions is unimaginable, a primitive civilization long past; yet there are people who remember life without cars, airplanes, insulin, movies, records, vaccines, telephones, radios, tanks and napalm! Looming within the lifetimes of our children are further accomplishments -- communication with extraterrestrial intelligence, fusion reactors, space colonies, weather control, complete mood control, intelligent computers, more drugs, more weapons and genetic engineering. Clearly the average person has a vital stake in scientific developments.

Nothing is more revolutionary than the ability to manipulate DNA, the very essence that defines the uniqueness of all species and individuals within a species. Several years ago, Rollin Hotchkiss one of the leading experts on the genetics of DNA wrote:

> "Many of us feel an instinctive revulsion at meddling with the finely balanced factors that make an individual what he is. Yet I believe it will surely be done or attempted. The pathway will be built on a combination of altruism, private profit and ignorance."

To which Philip Abelson, editor of Science replied:

> "I agree. Geneticists will have high ideals for the application of their knowledge. In practice, power to apply that knowledge, as was the case with nuclear energy, will come to rest in other hands."

I believe that we are all contributing the tools to a technology that will ultimately be used to alter the human genotype. Who will do it; on what scale; why will it be done? I don't know. The current interest in sociobiology; race, social class and IQ, innate aggressiveness and territoriality suggest a social climate in which genetic engineering might be acceptable. Suppose, for example, you were told that there is a genetically-distinct class of people who from the moment of conception can be predicted to have a high probability of never completing high school, of having IQs below 100, of being economically impoverished, malnourished, involved in crime and dying prematurely. Humanitarian and economic justification for genetic intervention could be advanced, but this description fits Blacks in ghettoes and Native Americans on some reserves. Here clearly the racial genotype is not the <u>cause</u> of the tragic prognosis, rather it is the societal conditions. But will we find it expedient to solve racism by tampering with race rather than changing social attitudes? In the same way, I don't find it far out to foresee the accumulation of a toxic pollutant that is intractible to clean-up (perhaps PCBs will be a case). It could be proposed

that a gene be introduced into people that will detoxify the contaminant. Will we find it cheaper and easier to modify people to tolerate higher levels of environmental pollutants than cleaning up? There is already ample evidence to suggest the answer is yes.

I fear these scenarios, not because tampering with the human genotype is a sin against God or an unnatural act. Rather, it is because humans have had a history of inventing very powerful tools and technologies without the wisdom to use them properly. I do not mean to impugn the motives or good intentions of any scientists. But history clearly shows us the misguided way scientists have acted because of their limited vision, their own self-interests and their ignorance.

Let me illustrate the social context within which developing DNA technology must be assessed. Here are excerpts from three articles written by a nationally syndicated newspaper journalist in Canada.

> "In Man, God is striving, through the process of Evolution to isolate the seeds of Superman; and the birth of Superman will herald the dawn of heaven on earth....Eugenics, after years of vilification as Fascism's means to a master race, will be universally accepted as the expression of a civilized scientific faith in divine force."
> Vancouver Sun, August 12, 1977.

> "Why after 30 years of welfare statism in the West, are the poor still with us? Because politicians define poverty as lack of money when in fact it is a congenital ailment."
> Vancouver Sun, September 13, 1977.

> "...geneticists are acquiring the means to transform men into leaders wise enough to become the founders of heaven on earth.... We are in a terrible left-liberal mess because we continue to breed like rabbits, ignoring the presence within us of a God who not only beseeches us, but gives us the means, to breed like supermen." Vancouver Sun, November 19, 1977.

I needn't belabor the way that science affects people and the way research percolates often in unexpected ways through different areas of society. The question is what am I recommending?

1) I think it's far too late to consider further moratoria on recombinant DNA experiments, nor do I think there should be. I congratulate NIH for its initiative and leadership in establishing guidelines and in taking the entire issue so seriously. A priority for all scientific organizations should be the education of the general public about the nature of the scientific venture. I have done many person-on-the-street interviews and am appalled at the public ignorance about science. The ready popular acceptance of Uri Geller, UFOs, plant communication, Chariots of Gods, Bermuda triangles, etc. in spite of the highest degree of education ever achieved attests to the failure of the scientific method to become a part of their lives.

I blame the scientific community for this public ignorance. Traditionally, "popularizers" of science are regarded by scientists as third rate intellects in a vulgar activity. Science has been mystified by a wall of jargon, technical know-how and expertise. That must change if the public is to understand the nature of the forces changing their lives and to appreciate the cultural role of science. A public educated in science will be a more responsible public, a less impotent public, that will at the least, demand that its candidates for office have positions on scientific issues.

In Canada (and I'm sure in the U.S.), the average person watches 5 to 6 hours of television a day! Yet if one were to try to determine the relative position of science from the amount of science programming, it's clear why the public is uninformed. If most of the information people are getting comes from television, then that's where effort should be expended. In Canada, 2 of the six highest rated programs on the public network, CBC, are science shows. I have absolutely no doubt that science programming could be very highly rated.

2) The education of prospective scientists must be broadened to include history, arts and philosophy. We must do something to break the trend for greater and greater specialization.

3)There should be complete public information about the use of recombinant DNA in industry and government such as the military. This must be legislated and enforced.

4) There must be a permanent body made up of scientists, lay people, politicians, and other groups who will study trends in science and organize symposia and papers on the social implications.

To conclude, we ought to consider Theodore Roszak's description of Mary Shelley's "Frankenstein" as an allegory for modern genetics:

> "Where did the doctor's great project go wrong? Not in his intentions which were beneficent, but in the dangerous haste and egotistic myopia with which he pursued his goal. It is both a beautiful and a terrible aspect of our humanity, this capacity to be carried away by an idea. For all the best reasons, Victor Frankenstein wished to create a new and better human type. What he knew was the secret of the creature's physical assemblage; he knew how to manipulate the material parts of nature to achieve an astonishing result. What he did not know was the secret of personality in nature. Yet he raced ahead, eager to play God, without knowing God's most divine mystery. So he created something that was soulless. And when that montrous thing appealed to him for the one gift that might redeem it from monstrosity, Frankenstein discovered to his horror that, for all his genius, it was not within him to provide that gift. Nothing in his science comprehended it. The gift was love. The doctor knew everything there was to know about his creature -- except how to love it as a person."

UNIVERSITY OF MINNESOTA
TWIN CITIES

Boynton Health Service
410 Church Street S.E.
Minneapolis, Minnesota 55455

January 9, 1978

Donald S. Fredrickson, M.D.
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This is to follow-up on your request at your advisory committee meeting on December 15 and 16, 1977, for comments on the proposed revision of the NIH Recombinant DNA Guidelines, printed in the September 1977 "Federal Register." I appreciated the opportunity to participate on the advisory committee and am particularly grateful to be able to provide a somewhat more thoughtful analysis of the proposed guidelines, after having had some time to reflect upon the proceedings of the meeting.

The following are my comments and suggestions, proceeding from the more general to the more specific:

1. OVER-ALL IMPRESSION ABOUT PROPOSED CHANGES- Although I will provide some specific suggestions later, I generally concurred with the proposed changes in the guidelines. I make this statement because I feel, on the basis of information presented by various witnesses (both for more stringent and less stringent guidelines), that the current recommendations for changes in guidelines represent a very cautious and small step toward relaxation of containment requirements.

2. THE ACUTE NEED FOR RISK ASSESSMENT EXPERIMENTS- Although it is not completely clear to me from the committee deliberations, it appeared that substantive risk assessment experiments have not gone forward because of some problems with unrealistic requirements in the present guidelines. It seems to me that risk assessment experiments are extremely important for the following reasons: (a) protection of the public from hazards which may exist with the new technology; (b) establishing public confidence in the scientific community's understanding of potential hazards associated with this new technology; (c) providing for the orderly progress toward future revisions of these guidelines; and (d) eventually reducing the cost of this research. It is my perception that your opportunity to prudently apply the variance provision in the proposed guidelines will remove a significant barrier now preventing conduct of risk assessment experiments. I believe this adds considerable incentive for adoption of this provision of the proposed guidelines.

A further word about cost of research; it seems to me that the economic implications of not knowing a risk are significant. As I was reflecting upon this,

I recalled a rather detailed survey I did of the lunar receiving laboratory several years ago to analyze human and mechanical failures in containment. Among some other observations, I was impressed with the financial implications of not knowing risk; it was extremely expensive to bring in scientists from long distances to work in this heavily-monitored, high-containment facility before there was an appropriate assessment of risk. After there was an appropriate assessment of risk, the work on "moon rocks" proceeded much more rapidly in a variety of locations throughout the country. In concluding, I strongly concur with the flexibility provided in the proposed guideline for prudent granting of variances to conduct risk assessment research.

3. DEFINITION AND ELIMINATION OF P-1 CONTAINMENT CATEGORY- I would agree with the new approach to the definition of recombinant DNA, as discussed by Dr. Maxine Singer; that is to define recombinant DNA molecules as novel or non-novel and to include synthetic molecules. The revision of this definition in combination with the section on containment provides an argument for deletion of the P-1 containment category. I suggest this because it seems to me that most of the research which would be done in the P-1 category of containment is that which would be defined as non-novel. Since this research would no longer fall under the guidelines, there would no longer be a need for the P-1 containment classification.

Also, it seems to me that there are other arguments for eliminating this category of containment. Without P-1 the NIH guidelines would have categories of containment more consistent with those for viral oncology studies and research with other hazardous biologic agents. Also, from Dr. Barkley's discussions, it appears that we would be more consistent with the European countries. In addition, elimination of P-1 would take into account the suggestion in the EMBO telegram that mouth pipetting not be permitted in recombinant DNA research. It should be made clear that my suggestion for eliminating the P-1 category does not imply a relaxation of containment requirements for P-2.

4. STRENGTH AND UNIFORMITY OF BIOHAZARD COMMITTEES- It is important that there be a great deal of confidence in the operation and processes of our institutional biohazards committees. There was an analagous situation several years ago when radiation committees had to undergo the same "growing pains" which biohazards committees are now undergoing on college and university campuses throughout the country. I believe that from the standpoint of efficiency, efficacy and public confidence in these committees, it is important that there be uniformity of effort from campus to campus. To assist biohazards committees, I would recommend an additional appendix in the guidelines to provide guidance for implementation of some of the provisions in the section on institutional roles and responsibilities. This appendix could include some further, more specific recommendations on such matters as medical surveillance and the means for institutional biohazards committees to certify that laboratory workers have received adequate training.

5. GUIDANCE FOR SELECTION OF VARIOUS COMBINATIONS OF PHYSICAL AND BIOLOGICAL CONTAINMENT- As I refer to the matter of appendices, I was pleased to hear of your intention to include a revised form of Appendix D. The proposed guidelines provide (Table I) an opportunity to select from various combinations of physical and biological containment for a particular experiment. From Dr. Barkley's discussion, it was clear to me that the investigator and the biohazard committee should apply some judgment regarding the most appropriate selection for combination of physical and biological containment. For example, Dr. Barkley used a particular illustration to demonstrate differing combinations of the most appropriate containment

depending upon the pathogenicity of an organism to animals outside the laboratory, versus pathogenicity to a laboratory worker. I would be in favor of continuing with the idea of options for physical and biological containments. However, Appendix D should provide guidance for use of this table by the principal investigator or the institutional biohazards committee.

6. EMPHASIS OF POSSIBLE FUTURE REGULATORY AGENCY- Since Mr. Hutt and others brought up the matter of future regulation, I would like to add some thoughts regarding design of this process. I think it is important that the staff in the regulatory agency which will be charged with this responsibility have a basic understanding of recombinant DNA technology, so that when regulations are enforced, there can also be consultation on how to meet the regulations. In particular, there should be an understanding of matters related to communicable disease control and epidemiology, containment techniques, and good microbiological practice in laboratories. The suggestion was made by some witnesses that the agencies' knowledge to regulate should take precedence and that the technical matter can be learned, or additional staff can be hired with appropriate technical knowledge. In this instance, I would suggest that it is more important to select an agency with the technical understanding of such matters as I described above. If there is need for additional understanding of the regulatory process, possibly this could be obtained by consultation with other regulatory agencies. In concluding my comment, I would like to state that I am not speaking in strong preference for one agency or the other, but rather for a principle; whatever agency regulates, considerable effort needs to be made to provide consultation along with enforcement.

7. POSITION AND RESPONSIBILITIES OF THE BIOSAFETY OFFICER- As stated in my remarks during the meeting, I am in accord with the concept of a biosafety officer. I also agree with the flexibility provided in the guideline for the appointment of this person. However, in accordance with the comments of others, possibly there should be a footnote in the guideline which establishes the principle that this person not be involved in the conduct of research related to his or her responsibilities as a biosafety officer. If possible, this concept could be established in a general way so that it could apply on our campuses to other biosafety concerns.

In regard to the description of the duties of the biosafety officer, I feel the emphasis is too much on the regulatory aspects of this position and not enough upon the consultative. The only duty which leaves a role for consultation relates to security, whereas I would suggest that perhaps the greatest opportunity which this person would have to provide a more fail-safe environment in which to conduct research relates to the areas of consultation and training. Although I can cite numerous instances where this might occur, one of the most effective has been for our biosafety officer to consult directly with the investigator as the experimental protocol is designed to assure safe microbiological technique. In many instances this not only assures safe technique, but also introduces ideas for improvement of technique, which increases the reliability of experiments. Consequently, I would recommend that the last duty of the biosafety officer be revised to read: "Provide consultation on such matters as preparation of memorandums of understanding and agreement, development of an emergency plan, design of experiments for physical and biological containment, and laboratory practices related to conduct of the research."

8. EXTENT OF EMERGENCY PLAN- I believe one can interpret the preparation of the emergency plan to relate only to what happens if spills occur within the laboratory. I would suggest that the concept of emergency plan be broadened by addition

of a footnote which references such matters as fire, either in the laboratory or in other parts of the building, and responses related to natural disasters, such as earthquakes or tornadoes. I do not believe this has to be spelled out in detail. However, similar to laboratories using radioisotopes, the investigator and the institutional representative should be prompted to think through how to handle these types of crisis.

9. AUTOCLAVE LOCATION IN P-3 LABORATORIES- A comment was raised both in the letters to you about the guidelines and in the advisory committee meeting about the autoclave requirement for P-3 facilities. Should it be in the controlled area of the P-3 laboratory or should it, as stated in the proposed guidelines, "be available in the same building in which organisms containing recombinant DNA molecules are used?" From an operational viewpoint, I would suggest that the closer the autoclave can be to the point of generation of the solid wastes, the more likely we are not to have breaches of this provision requiring decontamination of wastes. I am particularly troubled by the term "same building," since in our sprawling medical research complexes, often involving many hundreds of hospital beds, that could mean transport of wastes a considerable distance via some rather sensitive patient areas of the institution. If it is inappropriate to require that the autoclave be within the controlled area of the P-3 facility, I would suggest some change in wording to reflect a "location convenient and in close proximity" to the controlled area. Even more explicit language would be desirable.

I hope you will find the above comments of help as you undergo this important task of revising the recombinant DNA guidelines. As I am sure is quite evident from the early portions of my discussion, the balance of the stringency of guidelines with the realistic assessment of risk (at this point potential risk) will place myself and others in similar positions on campuses throughout the country in a much more comfortable "environment" in which to implement these guidelines. I feel a realistic assessment of risk will help us maintain our credibility with the public and outside agencies on the one hand, and with the investigators in the various academic units on the other.

Again, thank you for the opportunity to participate in the process of revising the recombinant DNA guidelines.

Sincerely,

Roger L. DeRoos, Ph.D.
Director

Department of Environmental
Health and Safety
Boynton Health Service

RLD:mlo

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOCHEMISTRY
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Area Code 415
497-6161

January 10, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing to urge you to promote the immediate development of a bakers' yeast cloning system. Such a system will most likely become the safest and most versatile of all the cloning systems.

I was involved in several informal discussions at the 1975 Asilomar Recombinant DNA Conference and at the 1976 San Diego Biohazard Assessment Meeting concerning the development of a bakers' yeast cloning system. At that time, however, there were a number of technical problems that required attention. My laboratory and others have, since then, worked on solutions to these problems (i. e., selective marker, DNA transformation system, etc.). For the most part, they have been solved, and I believe a bakers' yeast cloning system can now be developed within the next few months. I find this an urgent matter since most of my research is becoming totally dependent upon such a cloning system. For some experiments we could, however, use transformed tissue culture cells, although I am reluctant to take this approach because I feel it exposes workers in my laboratory to greater risk than is necessary. Below, I have outlined some of the advantages and safety features inherent in a bakers' yeast cloning system.

1. The bakers' yeast that would be used (Saccharomyces cerevisiae) are laboratory strains that have, like E. coli K12, been in captivity for several decades. Therefore, many of the properties that make E. coli K12 a moderately contained strain also apply to bakers' yeast.

2. Like E. coli K12, none of the laboratory strains of bakers' yeast are totally wild type but have various defects that would severely cripple them in a completely natural environment.

3. Unlike E. coli, none of the naturally occurring strains of S. cerevisiae are pathogenic to man, animals, plants, or any life form (Rose and Harrison, 1969). Furthermore, none of their close relatives are pathogenic.

4. Unlike E. coli, S. cerevisiae is only found to thrive in an environment where there is a high sugar content and a low temperature (DoCarmo-Sousa, 1969; Yoneyama, 1955, 1956, 1957a, b; and Lund, 1954).

5. Unlike E. coli, there are no viruses of S. cerevisiae. Very extensive searches have been made for such viruses.

6. Unlike E. coli, there are no plasmid-type DNA transfer systems in S. cerevisiae.

7. Because of points 5 and 6, the cloned recombinant DNA of S. cerevisiae is very unlikely to be disseminated to other organisms. S. cerevisiae is unique in this respect, and in fact, this property has been the biggest block to the development of a bakers' yeast cloning system.

8. The products of bakers' yeast are non-toxic. In addition to being a major ingredient of health foods, it is also found in bread, cake, and other baked goods, as well as in beer, wine and other drinks.

The above points illustrate that a bakers' yeast cloning system is likely to be the safest possible approach. It is inconceivable that yeast can be dangerous. We have been ingesting large amounts of yeast and yeast products for more than 10,000 years.

On the following page, I have listed some references you might find useful.

Sincerely yours,

Ronald W. Davis
Associate Professor of Biochemistry

RWD/lh

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January 11, 1978

Scott Thacher
28 Munroe St.
Somerville, Mass. 02134

Dr. Donald Frederickson
National Institutes of Health
Bethesda Maryland.

Dear Dr. Frederickson:

I was grateful for the opportunity to participate in the open NIH hearings on December 14 and 15, 1977, on proposed new guidelines for recombinant DNA research. At that time I criticized the NIH for not appointing a guidelines committee which was not more representative of scientists' and non-scientists' views. Here are my criticisms and suggestions in more detail.

1) Include non-scientists, and scientists in fields not closely related to recombinant DNA research, in deliberations from the beginning of any revisions of the guidelines. The guidelines committee had little such perspective and, indeed, was not even representative of the feelings of molecular biologists themselves on the caution required for evaluating the research. A successful effort to have primarily non-scientists take part in deliberations on research safety can be seen in the report of the Cambridge Experimentation Review Board (Bulletin of the Atomic Scientists, May 1977, p. 2). This group showed that in a few months they could grasp and responsibly evaluate the consequences of recombinant DNA research and make suggestions for safety regulations that are still being debated nationally -- for example, whether to institute a program to maintain for many years the health records of workers who have been in recombinant DNA laboratories. Non-scientists must be given long-term involvement in these discussions so they can educate themselves enough to challenge some of the assumptions made by scientists more deeply involved in the field of recombinant DNA research.

2) The NIH should take nominations for this committee from the following groups who have showed concern over regulation of the research: several labor unions, including the Oil, Chemical, and Atomic Workers' and the AFL-CIO; environmental groups such as Friends of the Earth, the Sierra Club, the NRDC, and many others; involved and knowledgeable community governments such as in Cambridge, Mass., and Ann Arbor, Mich; and groups of science activists such as Science for the People and the Coalition for Responsible Genetic Research. Statements of the nominees should be part of the public record, followed by public hearings on their selection. A brief resumé of the qualifications and activities of the committee members should be included with guidelines which they write. It was disturbing that the proposed revised guidelines did not even show the committee members' names.

3) The Advisory Committee to the Director of the NIH, brought together just for these hearings, was the most broadly representative group of non-scientists to consider the research for the NIH so far. Their effect is certain to be not much more than token, however, since the tenure of most of the committee members was limited to the two days of the hearings. The formation of such a committee, with little ability to follow up on its recommendations, whitewashes the more difficult problems of involving interested parties, only a sampling of whom are given in paragraph two, in the direction of scientific research and its regulation.

Scott M. Thacher

Scott M. Thacher Graduate student, Committee on Higher Degrees in Biophysics, Harvard University
Member: Science for the People, 897 Main St., Cambridge, Mass. 02139

Department of Microbiology
Oregon State University
Corvallis, Oregon 97331
USA
(503) 754-1441

12 January, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I want to express my gratitude for having the opportunity to participate in the meeting of the Advisory Committee to the Director last month. I was pleased to witness the degree to which the several sides of questions concerning the proposed revisions to the Guidelines were so thoroughly presented and discussed. The expeditious yet fair treatment of all testimony was evidence for the success of the meeting.

It is my belief that the proposed revisions, as published in the Federal Register, 27 September, 1977, would facilitate in vitro DNA recombination experimentation without increasing the degree of risk from that inherent in the procedures prescribed in the present Guidelines. I do not favor their wholesale adoption, however. It seemed evident at the time of the meeting that some changes would be made; rewriting the definition paragraph of the Introduction to include chemically synthesized DNA molecules is an example.

The testimony of several witnesses and statements made by some committee members suggested that a reconsideration of the very high containment levels required for some experiments involving the cloning of DNA from viruses of warm-blooded vertebrates was in order. If it is the consensus of the appropriate members of the NIH Recombinant DNA Molecule Program Advisory Committee that proposed levels of containment for these experiments owe their existence more to political considerations than to scientific ones, as was implied by some testimony, I hope that the feasibility of making the containment requirements less stringent will be re-examined.

Similarly, it was suggested that increasing the containment required for cloning genes from Agrobacterium tumefaciens is unjustified, considering the scientific information available. If the Recombinant DNA Molecule Program Advisory Committee determines that those suggestions are valid, I hope that will be reflected in the Revised Guidelines by permitting these experiments to continue at the P2 level.

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While there were many other valid recommendations made to you concerning the proposed revisions, they are present in the record of the meeting and I shall not restate them in this letter. There are, however, some specific points I would like to make regarding the section on Roles and Responsibilities in the Proposed Revised Guidelines; some of these I included in my statement to you during the meeting and others have come to mind since that time.

In the section describing the roles and responsibilities of the principal investigator (Section IV A. (v)), I feel the Guidelines should be more specific in delineating exactly what the investigator must do to secure approval for his proposed research. If he must submit his draft of a Memorandum of Understanding and Agreement to the NIH Office of Recombinant DNA Activities, the Guidelines should include a statement to this effect and go further to define what information comprises an acceptable MUA (perhaps the latter statement could be included as either a footnote or an appendix).

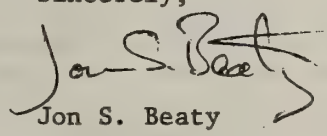
Also, the Guidelines should inform the investigator of the vehicle by which the ORDA will either affirm or deny his request; will a telephone conversation be sufficient or must he await a formal letter or a revised notice of his grant award or continuance before initiating any recombinant DNA experiments? While these may seem to be rather picky recommendations, misunderstandings have occurred regarding this matter and I believe specific procedures must be described in the Guidelines.

Likewise, in regard to institutional roles and responsibilities (Section IV B.), the role of the institutional biohazards committee in authorizing an MUA before submitting it to the ORDA is not at all clear. Does the institutional biohazards committee have this responsibility and, if so, what specific procedures must be followed? The Guidelines should answer these questions.

Footnote 9 of the Proposed Revised Guidelines raises the possibility of establishing an area biohazards committee. Is it conceivable that both an institutional committee and an area committee could be monitoring the activities of the same investigator, resulting in a potential conflict of jurisdiction? Perhaps the intent of this footnote could be clarified.

I hope that you will find these comments useful. I am impressed by the overall direction of change in the proposed revisions and am looking forward to further reduction of stringency in the Guidelines as may be warranted by accumulation of new risk assessment information.

Sincerely,



Jon S. Beaty
Member, OSU Biohazards Committee

cc: Dr. Waclaw Szybalski

Laboratoire Européen de Biologie Moléculaire
European Molecular Biology Laboratory
Europäisches Laboratorium für Molekularbiologie

From the Director-General
Sir John Kendrew

13 January 1978

Dr D Frederickson
National Institutes of Health
Building 1, Room 124
Bethesda MD 20014
USA

Dear Don

I am writing, as you requested, to give my overall view of the proposed revisions of the Guidelines for Recombinant DNA research, in the light of the public hearings on 15 and 16 December last. I should first like to express my gratitude to you for your invitation to me to serve on this occasion as a member, and indeed the only non-American member, of your Advisory Committee. The opinions set out in this letter do not differ from those I expressed verbally during the closing session of the Committee on 16 December.

The Proposed Revised Guidelines represent a significant downgrading of the containment requirements for different classes of experiment. I find the evidence that led your Committee to propose this downgrading very convincing, and I am persuaded that the revisions represent a step in the right direction. The extent of the downgrading is, of course, a matter for judgement - the phrase "to err on the side of caution" has been used, and it evidently reflects the fact that there is still public concern, and whether or not this concern is justified it is certainly real. On the other hand it is useless to issue strict guidelines unless these have the respect of the scientific community. Evasion is easy, and the guidelines will not be followed unless they are thought to be reasonable. In the light of these conflicting tendencies (neither of which can be quantified by any amount of scientific argument) your Committee has proposed a step in the direction of relaxation.

Here we should note that, if what your Committee has proposed represents one step of relaxation, then in Europe both the EMBO Committee and the French authorities have made proposals that could be regarded as two steps in the same direction.

My personal judgement is that, viewed strictly from a scientific viewpoint, the further steps of relaxation proposed in Europe are justified; that is, the revised NIH guidelines are still unnecessarily strict. However, I accept that the decision must be a function of the degree of public concern as well as of a purely objective assessment of risks. Against this background I find the NIH proposals perfectly reasonable.

Returning to the question of activity in this field in Europe and elsewhere, it is certainly very desirable that the practices in different countries should be harmonized. The United States has provided leadership in this field, and therefore I think it particularly important that there should be close liaison between the responsible groups in the United States and elsewhere. The joint NIH/EMBO Workshop on "Parameters of Physical Containment", held in London in March 1977, was an important step in this direction, and I very much welcome the decision taken during your hearings last month, that there should be a similar joint study of virus classification.

At the world level the International Council of Scientific Unions has now established its Committee on Genetic Experimentation, and I am particularly happy to note the very active part being played by American scientists in the work of this Committee.

Finally some miscellaneous points that occurred to me during the hearings, not all of them immediately relevant to the drafting of the guidelines:

1. The carrying out of risk-testing experiments should be encouraged, and in cases when special exemptions from the guidelines need endorsement this should be granted wherever possible. It is most unfortunate that an important risk-testing experiment planned in the USA was held up for administrative reasons.

2. The study of alternative host-vector systems should be encouraged. These will be increasingly needed, both in pure research and in industry, and the sooner they are certificated, the better.

3. High priority should be given to the organization of training courses in safety measures; and a system of validation of such courses should be developed.

4. Consideration should be given to setting up a system of certification of equipment used in high-security laboratories, and standardized test procedures should be developed.

5. More thought should be given to the role of positive pressure suits in work at high containment levels, possibly not only in a subsidiary role in a "specially designed suit area", but perhaps as a major element in the design of P4 facilities.

All good wishes for the completion of your study of the guidelines, and best personal regards.

Yours sincerely

John

UNIVERSITY OF CALIFORNIA, IRVINE

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DEPARTMENT OF CHEMISTRY

IRVINE, CALIFORNIA 92717

January 13, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20014

Dear Dr. Fredrickson:

I am writing to present my comments on the proposed changes in the NIH recombinant DNA research guidelines, as discussed in the December 15-16 meeting of the Advisory Committee to the Director, NIH.

Until recently I knew very little about the recombinant DNA controversy. Most of my original fears disappeared rapidly as I became better informed, and I now tend to agree with the consensus of the experts in the field, which appears to be that the original fears--say, of spreading an uncontrollable epidemic--were exaggerated. Several statements presented during the December meeting--such as those of Dr. James Watson, Dr. W. Szybalski and Dr. Bernard Davis--were rather convincing to this point.

On the other hand, there are numerous examples of situations where unforseen problems have arisen when scientific discoveries were applied on a commercial scale, perhaps as a consequence of the transition from science to technology (i.e., radiation damage, release of chemicals to the environment, etc.). In retrospect, the "experts" often took an overly narrow point of view as to the potential hazards associated with their activities. In the case of recombinant DNA technologies, one can easily imagine that problems might arise even before these technologies are exploited on a commercial scale because of the potential for self-replication; of course, the risk will increase with the rapid proliferation of these technologies, but the worry is that it is sufficient, in principle, for a single event--say, the accidental production through a contaminated sample of a small number of chimeric organisms which somehow manage to escape and reproduce in the environment--to have widespread and long lasting harmful effects on the ecosystem for which there might be no effective countermeasure. Among others, Dr. Robert Sinsheimer and Dr. Jonathan King articulated some of these possibilities, so that this type of worry is not unique to outsiders to the recombinant DNA field.

It seems to me that from a scientific point of view this general matter of risks to the environment--as opposed to some rather specific questions, such as

conversion of E. Coli K-12 to an epidemic pathogen capable of infecting a human being--has not been discussed sufficiently, and as such it is perhaps the weak point in the DNA controversy. Some experts appear to be convinced that this type of subtle hazards to the ecosystem are practically non-existing; they argue, for example, that recombinant DNA experiments merely duplicate events that occur extensively in nature. Others argue that the probability of creating harmful organisms which can survive, reproduce and adapt to the environment is greatly enhanced through this experiments. As an outsider to the field I cannot judge easily the scientific merits of each side of the argument. Is the current status of science in this field such that, indeed, very little, if anything, can be said about the seriousness of these risks? Or, are the risks so small that the scenarios involving appreciable perturbations to the ecosystem appear farfetched?

In my opinion, the nature of the situation, which involves imposing an involuntary risk to society, demands that the burden of proof lie on those members of the scientific community who maintain that recombinant DNA research is quite safe; they should provide convincing scientific (besides emotional) arguments in their favor. The Environmental Impact Statement on the NIH guidelines (October 1977) contains a brief discussion of possible hazardous situations (Section IV-C, pp. 23-31), and clearly the possibility of a harmful outcome of recombinant DNA research is not ruled out in that document. It states, for example, that "current knowledge does not permit accurate assessment of whether such changes will be advantageous, detrimental, or neutral, and to what degree, when considering a particular recombinant DNA experiment." (p. 23).

In terms of risk assessment, it is very difficult to deal with situations where the risk cannot be quantified, where even the very nature of the risk is not well defined, and where the probability of occurrence of an event harmful to the environment is admittedly small, but the consequences potentially quite serious. The only reasonable course of action is to proceed with caution and to try to be alert to unforseen consequences. I am, of course, assuming that the benefits of carrying out recombinant DNA research are potentially very large; otherwise there would be no need for society to incur even a small risk. Furthermore, I am not considering other issues which surfaced during the December meeting, such as the possibility of deliberate misuse of knowledge acquired through this research; knowledge in almost all branches of science can also be potentially misused.

What does all this imply in connection with the proposed revisions to the NIH guidelines? It seems to me that overall, the guidelines are drafted to a considerable extent from the point of view of protecting man from an epidemic, which is the hazard that now appears to have been exaggerated (perhaps the very purpose of the guidelines is not stated with sufficient clarity). Thus, the assignment of the various experiments to the many different categories appears somewhat arbitrary. In particular, the two extremes in the containment levels referred

to in the guidelines deserve comment. There does not seem to be enough justification to require containment levels which are practically unattainable at present for experiments such as the one proposed by Dr. Martin and Dr. Rowe (discussed at the December meeting) which is designed to provide much needed risk assessment information. Thus, the guidelines appear to be overly restrictive on that end of the scale. At the other end of the scale, the proposed revisions might be too little restrictive--particularly if one adopts the view that not all potentially serious risks have been clearly identified and quantified. The situation is complicated by the fact that there appears to be some confusion as to which experiments are to be excluded from the guidelines if the proposed revisions are adopted (i.e., it is not clear in all instances what is meant by "novel" or "not novel" recombinant DNA), as borne out by the statement of Dr. Mary-Dell Chilton. If indeed one is to proceed with caution, it would seem appropriate, in my opinion, not to exclude such a large number of experiments, but rather to modify the guidelines to cover these experiments with a much simplified administrative procedure, that is, not only calling for a low physical and biological containment level, but also for a low "bureaucratic" containment level; this extension of the guidelines should at least provide a more reasonable data basis for future revisions. Perhaps a simplification of the administrative procedures is also in order for those experiments which call for a P1 containment level under the proposed revisions.

There are some additional points which I consider relevant--points, however, that I will not further elaborate upon because they were discussed in sufficient detail by other members of the committee. To name a few, I share some of the concerns of Ms. Patricia King and Mr. Peter Hutt about procedural matters; I agree that appropriate training programs should be established; and I also believe that a special effort should be made to communicate to the public some of the rather complex technical questions raised by the recombinant DNA issue.

Sincerely,

Mario J. Molina

Mario J. Molina
Assistant Professor of Chemistry

MJM:mmg

Max O. Schultze, Apt. 211
2201 Ambassador Road N. E.
Albuquerque, N. M. 87112

14 January 1978

Dr. Donald Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Re: Recombinant DNA

In the January 9 issue of Chemical & Engineering News I have seen a report by Jeffrey L. Fox on the December 1977 meetint on revision of the NIH guidelines on recombinant DNA.

As a biochemist, now retired, I have followed the developments in this area with much interest and some concern.

It is timely, no doubt, to revise some of the current guidelines. I imagine that heavy demands are being made to relax the current restraints, based on claims of current evedence, largely unpublished, that the potential dangers have been exaggerated.

I believe that the restrictions now in force are generally sound and prudent and that they permit the accumulation of extensive and sound evidence which is so much needed before restraints are relaxed.

I am writing to urge that a very conservative and cautious stance be adopted while the proposed amendments are being considered. I trsut that severe penalties will be invoked against institutions in which violations take place.

Very truly yours,

Max O. Schultze

State of New Jersey

DEPARTMENT OF LAW AND PUBLIC SAFETY

JOHN J. DEGNAN
ATTORNEY GENERAL

OFFICE OF THE ATTORNEY GENERAL
STATE HOUSE ANNEX
TRENTON 08625

January 19, 1978

Dr. Donald Fredrickson
Office of the Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

At the Director's Advisory Committee meeting on December 15 and 16, 1977, you invited each committee member to submit his final thoughts to you in writing. What follow are mine.

Introduction

The Introduction to the Revised Guidelines ought to be far more extensive than it is now. It ought to contain much of the information set forth in the explanatory material sent to committee members prior to the meeting. The objective of the Introduction should be to reiterate how recombinant DNA organisms are produced. It should indicate why they are thought to be potentially dangerous and, therefore, an appropriate subject for regulation. Finally, it should convey a general understanding of how these guidelines differ from the set currently in use. All of this must be articulated in language able to be comprehended by the intelligent layman.

These suggestions are intended to emphasize the critical importance of communication. That there are inadequate conduits for the transmission of scientific information to the public is largely responsible for the sometimes violent and vitriolic reactions of certain groups to recombinant DNA research. A well constructed, simple and informative Introduction to the Revised Guidelines can attempt to dispel some of the crippling fear of the unknown which has hampered efforts to debate the hypothesized hazards of this research. Dr. Campbell's remarks at the December meeting, as amplified in his letter to you of December 27, ought to be considered here. I bow graciously to his criticism of my off-hand remark endorsing the notion that what is not novel is safe. He is perfectly correct that this is not the point. What the public must be given is some standard for comparison. It must understand that there is no evidence to suggest that nature will not be at least as likely a source of harmful

pathogens as researchers in this field. It must know that we have promulgated restrictive guidelines not to protect it from a known hazard, but to guard against the possibility that new organisms generated by this research could exert some harmful influence on us, and that we have taken these steps even though there is no firm theoretical basis for believing that such harm could result.

Physical and Biological Containment

These sections have been carefully and thoughtfully set forth in the Revised Guidelines, and I can add nothing to your consideration of them.

Experimental Guidelines

Based on the testimony presented at the December meeting, the assignments of physical and biological containment standards for plant and animal viruses ought to be reviewed by the Recombinant DNA Molecule Program Advisory Committee. These assignments appear to have been made on the basis of the Committee's perception of political acceptability, not on the basis of professional judgments as to risk. This is a great mistake and perverts the process of drafting guidelines. That process depends, in the first instance, upon obtaining expert advice as to risk from a professional panel unfettered by political constraints. This technical advice is then rendered to you so that, with the aid of your own advisory committee, you can assess that advice in light of broader considerations, such as public acceptability. If the technical advice you receive has already been diluted by political concerns, your task is made exceedingly difficult and the public is denied the opportunity of ascertaining who is making the technical assessments and who the political ones.

This difficulty may explain in part why the Revised Guidelines make containment assignments for virus studies which are not in accord with those made in Europe. If you were to arrange an early meeting with European scientists, these matters could be discussed, and it might be made clearer than it is now why our standards differ so from theirs.

A further difficulty with the Revised Guidelines, which they share with the original guidelines, is that the philosophy of assignment is not clearly set forth. Put another way, there should be a firm theoretical foundation for the assignment of physical and biological containment levels if, indeed, this is possible. This is particularly important because there is no present evidence that any of this research can create harmful organisms. In the absence of such evidence, the NIH should clearly state why it believes some experiments to be more hazardous than others, and why some experiments are banned.

Apropos of forbidden experiments, the provisions in the Revised Guidelines permitting certain of these experiments to be performed for the purpose of risk assessment are excellent. They eliminate the intolerable situation in which experiments thought to be dangerous were not permitted to be performed by anyone to ascertain whether in fact theywere dangerous. Furthermore, you should exercise this discretionary power to launch a program of risk assessment experiments.

In short, the Revised Guidelines must contain not only a well articulated theoretical base, but a device enabling you to test the assumptions undergirding this base.

Roles and Responsibilities

The assignment of primary enforcement responsibility to institutional or area-wide biohazards committees is clearly the best of the alternatives which I have heard discussed. Of particular note in this connection, are the portions of the Revised Guidelines which suggest that these committees should have members who are not scientists. As long as these are suggestions, I would recommend that some language be included encouraging these other members be drawn not only from the local community, but chosen after consultation with the municipal governing authority. These authorities have the ultimate responsibility for public health and safety, and those who serve on these authorities must be comfortable about what is being approved by the institutional biohazard's committees. Indeed, the appointment of someone like a public health officer, who is responsible to the local governing authority, ought also to contribute substantially to enhancing the quality of the communication between the researchers and the municipal governors.

As I have said much about communication with the public earlier, I will only add here that this subject would be the worthy object of an NIH sponsored conference. Keeping members of the public accurately advised about scientific developments is a problem that will not go away and which cannot be solved by the ordinary newspaper and magazine coverage.

Finally, on the subject of institutional biohazard committees, I wish to note that no discussion of enforcement is complete without mentioning sanctions. While the notion that scientists should be liable to pay huge fines for negligent violations of these guidelines is deplorable, there is no doubt that sanctions must be available. For NIH Grantees the withdrawal of grant funds ought to be a significant disincentive. Another would be the inability to publish the results of inappropriately conducted research in reputable journals. These penalties, implying the opprobrium of their peers, will always be coupled with the fear of legal liability for negligent conduct which causes harm to others. Taken together, this structure of sanctions makes the consequences of flagrant disobedience to the requirements of the guidelines an unattractive prospect.

As for privately sponsored researchers, inability to publish is not an effective sanction, and even when coupled with the exposure to legal liability may not be enough. Legislation is undoubtedly needed. It should require adherence to the guidelines, permit federal inspections, provide some structure of fines for disobedience, and preempt state and local legislation. Such legislation is not needed to protect the public from the conscientious industrial researchers whose companies have been voluntarily complying with the guidelines right along. It is needed to deter less responsible researchers from entering this field and destroying the reputations of those whose record to date is so good.

The preceding suggestions are based on the belief that peer review, coupled with some local oversight using national standards, is the appropriate enforcement philosophy for this research. It presupposes, however, the existence of guidelines which are scientifically reasonable since restrictions for which there is an inadequate rationale, encourage disobedience. Finally, it puts the burden of responsibility on the scientists where it ought to rest in the hope that it will act as a vote of confidence in their integrity. Because the scientists doing this research were the first to share its problems with the public, even though restrictions were sure to follow, they have earned our trust. We should not now reward that behavior by imposing such conditions on this research as might change the relationship between the scientists and the public from cooperative to adversarial.

I trust these remarks will be of assistance to you in continuing your exemplary efforts to accomplish the difficult task of drafting the Revised Guidelines. Thank you for the privilege of participating in the discussion concerning them.

Sincerely,

Dennis J. Helms
Special Assistant to the
Attorney General

DJH:lea

Statement to the Director of the National Institutes of Health following Public Hearings on the proposed revised Guidelines for Recombinant DNA Research. December 15 and 16, 1977

Rosemary Crone Menard
Special Member Director's Advisory Committee

Dear Dr. Fredrickson,

Once again, I would like to thank you for the opportunity to participate in the recent public hearings on the proposed revised Guidelines for Recombinant DNA Research. The diverse points of view represented by the committee membership and the invited and public witnesses expanded my understanding of the many issues involved in the recombinant DNA controversy. My background, experience and interests helped me focus on several issues which I will address here, and though I will generally avoid those highly technical points raised during the hearings, I am never-the-less concerned for their resolution. Public confidence and the respect of the scientific community depend on the satisfactory resolution of problems with the data base for the EK-2 host vector system and the methods used to calculate risks as examples of what I mean.

The issues I will address fall into three catagories: those of concern to a worker in the field of recombinant DNA, those of concern to a member of a biohazard committee, and those of concern to a private citizen whose involvement with the League of Women Voters and the local political scene color her perspective. I will proceed to the points I want to make grouping them as the order above indicates.

As one who works in the laboratory every day, I am concerned with the health and safety of not only myself but also of those working in a similar setting in general. I believe that a standardized training program for those working with recombinant organisms is essential. As this technology becomes a valuable research tool in areas where microbiological techniques are not commonly used, investigators need to have access to well established training programs to assure the safety of their staff and the community. Much of the responsibility for such training presently falls to the investigator and the variability which resulted is a good reason to ask institutions to take over this serious work. In addition, emergency plans which are required by the guidelines to plan for

clean up of major contamination of work area or personnel should be a required part of the investigators's MUA, should bear the signitures of laboratory personnel and should be approved by the local biohazard committee.

The laboratory setting can, at times, be a very isolated one. A good example is the research group at this university doing polyacrylamide gel electrophoresis and being unaware, as of six months ago, of the extreme toxicity of acrylamide. The point I want to make here is that information on real dangers may be so poorly circulated that even very careful people may suffer. Recombinant DNA work is only one kind of hazardous work, but no matter what the origin of the hazard, a "let the buyer beware" philosophy is unacceptable. One solution might be a newsletter (with references) for technical staff which would provide information to help them deal with the ever increasing barrage of chemicals, organisms and particles. (I would be happy to provide more ideas on this subject at your request.)

One last point I would like to raise is related to periodic inspection of all facilities for compliance with the guidelines. The idea of inspections doesn't particularly appeal to me, but I believe that because of the cohesive nature of laboratory groups, it is unlikely that violations will be reported by technical staff or graduate students. In my experience, regulations of the Occupational Safety and Health Act protecting workers' rights in such cases are generally unknown to staff people here. Thus I would favor inspections, certainly of P-3 facilities at least, to monitor compliance.

As a member of an institutional biohazard committee (IBC) attempting to implement the NIH guidelines, the elimination, to the greatest extent possible, of vague language from the revised guidelines would be a great service. A specific example involves the two references to work with naked DNA where more specific information on inactivation proceedures as well as using the same terminology to describe the required containment (minimal vs. P-1) for such work would be very helpful. The problems and pitfalls of interpretation mean that throughout the country a variability in application of the guidelines is bound to exist. Perhaps like many other institutions, the University of Washington initially adopted the NIH guidelines as the minimum standards for recombinant work here.

In light of the competative pressures under which most investigators work, significantly more stringent standards than those applied by NIH could very effectively hobble any research project just as a more lenient interpretation could give a significant advantage to a researcher. Because of the proposal in the revised guidelines to allow IBCs to lower containment levels one step (physical or biological) under certain conditions, the problem of variability in application of the guidelines becomes even more serious. I believe that more specific directions from NIH to the IBCs along with establishing a communication network among IBCs are two viable approaches to help alleviate the problem. In any case, more and better communication and information exchange between IBCs would allow them to help each other by exchanging ideas on prodeedure, technical materials and references, and training and safety information and should be encouraged and facilitated by NIH.

Prior to any further revisions of the NIH guidelines, I would like to suggest that the IBCs be polled via a questionaire to determine the most common problems they encounter in discharging their duties as well as asking for suggestions on how to simplify their task, make it more meaningful or less frustrating.

My concerns as a private citizen are severalfold. Perhaps foremost is that of the role of the public in the decision making process. To my knowledge, recombinant DNA is the first technology in which the public has been involved from the very early stages. Initial public concern was largly that the technique would be used to accidently or deliberately create a "super bug" which could cause an epidemic. I perceive public concern in the Seattle area to no longer be focused on the epidemic possibility but to have turned to the use of recombinant DNA technology to generate sufficient information to make human genetic engineering a reality. I believe that public involvement now means a more educated public who will be infinitely more capable of dealing with the obvious risks and benefits of human genetic engineering. By dealing with the risks and benefits of human genetic engineering, I do not mean accepting both without question, rather I mean participating fully in the decision making process by being involved in goal setting, policy making and general allocation of funds. I believe the same role should be open to members of the public now, and that it

is precisely because of the potential of recombinant DNA technology to lay the foundation for human genetic engineering that the present process should continue to be open and responsive to the public. I think that the composition of the Research Advisory Committee should remain as it now stands but that the work of the RAC should reflect a constantly evolving process of goal setting and policy making in which the public has full representation.

Finally, I have three concerns which stem from an apparent adoption of a narrow view. First, the narrow definition of the types of experiments covered by the NIH guidelines exclude possibly hazardous work in other areas, for example, cell fusion and somatic cell hybrids. While it is understandably desirable to limit what is regulated as much as possible, the point of regulations at all is to protect workers and the environment from possible harm. I think that some consideration of action to provide information type guidelines for any work of a hazardous nature is in order.

Second, testing recombinant organisms, hosts and vectors for pathogenicity should be carried out for as broad a species range as feasible. Humans are not the only hosts of value. Ecosystems are delicately balanced and an accidental disruption may not be easily returned to normal. Certainly there are limits to how much we can manipulate the environment, and it is wise to remember our limitations in situations similar to this.

Lastly, use of recombinant DNA technology brings us to a new era in science, and it seems important to me to utilize all the tools available to us to make the best use of what we learn. New methods for risk and technology assessment offer new perspectives on the problem and could be of invaluable assistance as we try to accomplish our goals.

Again, thank you for a very educational and enjoyable experience.

Sincerely yours,

Rosemary Crone Menard

Rosemary Crone Menard

The Connecticut Agricultural Experiment Station

123 HUNTINGTON STREET BOX 1106 NEW HAVEN, CONN. 06504 (203) 789-7258

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26 January 1978

Dr. Dewitt Stetten, Jr.
Deputy Director for Science
Office of the Director
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Stetten:

Several plant scientists have recently approached us concerning hazard assessment of plant pathogens as they pertain to the revised Guidelines. For shotgun experiments, all prokaryotic plant pathogens are lumped with Class 2 animal pathogens necessitating a P3 + EK2 categorization. This is certainly arbitrary and could be unnecessarily restrictive for many plant pathogens. Moreover, all plant virus DNAs as vectors are classified P3. In view of the fastidious requirements for transmission of DNA plant viruses and the lack of evidence suggesting they are a serious danger we think P3 is also unnecessarily restrictive.

Dr. C. I. Kado and three of his colleagues at Davis (in a letter to the Director, dated 12/5/77) have suggested a scheme for hazard classification of bacterial plant pathogens. This scheme could be a starting point for a discussion of the hazard classification of all types of plant pathogens, not just bacteria. We think the time has come for us to face this issue, as hazard assessment will certainly enter into the use of recombinant DNA with plants and their pathogens. We are not entirely convinced that we can devise a meaningful scheme but think we should try. If this is in order we would like The Recombinant DNA Committee at its next meeting to consider providing sponsorship for a group of concerned plant scientists to consider these issues.

With best wishes,

Yours sincerely,

Peter R. Day, Head
Department of Genetics

PRD for Milton Zaitlin

Milton Zaitlin
Professor

PRD/ebb
cc: Dr. C. I. Kado
Dr. Herman Lewis

MIdway 2-7124

Katharine R. Sturgis, M.D.
349 Wister Road
Wynnewood, Penna. 19096

January 28, 1978

Dr. Donald S. Frederickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

Enclosed is my opinion regarding the proposed revision of the First Guidelines. May I compliment you on the dispassionate manner in which you conducted the December hearings. They provided adequate confirmation of the thoughtfulness of the revision. So far as I am concerned, the relatively minor adjustments that seem indicated could be made now if they would not delay adoption of the revision or could be included in the next revision.

I hope this is in time to be helpful. The severe wintry weather caused numerous minor catastrophes which resulted in delays. To one of your vigor and skiing propensities, I'm sure the snow was taken in stride!

Warm regards to you, your wife, and Roberta.

Cordially,

Katharine

KATHARINE R. STURGIS, M.D.

Enclosure

KRS/s

The first Guidelines promulgated by the NIH were drafted for the emergency situation in which research on recombinant DNA was being contemplated or conducted independently in various laboratories. They have turned out to have been excessively cautious. This was commendable for the sudden new situation which confronted science. In view of the consensus of scientists that the first Guidelines are too stringent, a revision is in order. The proposed revised Guidelines published in the September 27, 1977, Federal Register and the testimony presented by individuals and members of the Advisory Committee to Dr. Frederickson on December 15th and 16th have convinced me that:

1. Adoption of the proposed revised Guidelines is wise and indicated.

2. Since periodic future reviews and revisions are provided for, it would be unwise to delay adoption while considering further more sweeping easing of the original recommendations.

3. Consideration should be given to a number of suggestions such as some from the Embo Advisory Committee (Document 32, Comments) like the possibility of extending trade-offs to P_2 and P_3 physical containment.

4. Plants should be included.

5. While experimental results to date have not revealed any cause for alarm, we are still in a state of relative ignorance; it may require generations to fully assess the impact of recombinant DNA on health, genes, and the environment. Methods for gathering data for subsequent evaluation should, therefore, be established as soon as possible as a sound basis for future revisions.

6. Industry should be formally brought under the Guidelines and provision should be made to respect confidentiality when necessary for the protection of private enterprise.

I do not favor police duties for NIH. Compliance should be the responsibility of some other governmental agency.

Katharine Boucot Sturgis

Katharine Boucot Sturgis, M.D.

SLOAN-KETTERING INSTITUTE *for* CANCER RESEARCH

DONALD S. WALKER LABORATORY, 145 BOSTON POST RD., RYE, N.Y. 10580 OWENS 8-1100

January 30, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Periodic updating and reconsideration of the Guidelines for recombinant DNA research is a necessary activity and we are glad to see that the process is taking place. The Guidelines address themselves to only one facet of the recombinant DNA question, however, and many members of the scientific community feel that there are broader issues to be considered. Unfortunately there has been no opportunity in the recent hearings on Guideline revisions to address these questions. I would like to point out three fundamental problems which are of serious concern to a number of us. These broad problems do not entirely fall within the purview of the NIH and would be more properly addressed by legislation. They are:

1. The responsibility for formulating, revising and granting exemptions from the Guidelines is vested in a small group, within the NIH, which is oriented toward biomedical research. Although the Committee is free to consult experts in other fields, there is no mechanism for assuring comprehensive and committed consideration of potential problems that could result from recombinant DNA technology in other areas, such as ecology. One cannot expect ecologists and others who are not now professionally involved with recombinant DNA to be sufficiently cognizant and committed to analysing the problem unless they are officially recruited and charged with public responsibility. Some means is also needed for integrating the views of the various experts so that the public interest will dominate. In short, since the NIH is a specialized body concerned with the development of the biomedical sciences it is inappropriate for dealing with the regulation of recombinant DNA activities.

2. Universal application of the Guidelines, and a method of enforcement, are lacking. Without these the Guidelines cannot be really meaningful.

3. No controls have been set up governing the future non-research usages of recombinant DNA technology. Although the NIH offers to seek the concurrence of other concerned government agencies before granting permission for release of recombinant organisms into the environment, this arrangement is far too loose and casual. The public interest requires a concerted study of the potential dangers of every proposed industrial application of the technology, before it is undertaken, as well as continued monitoring. Because of the large scale of industrial technology as opposed to research,

(Continued)

SLOAN-KETTERING INSTITUTE *for* CANCER RESEARCH

DONALD S. WALKER LABORATORY, 145 BOSTON POST RD., RYE, N.Y. 10580 OWENS 8-1100

this is true whether or not the industrial use involves intentional release of the organism. Often it will be necessary to make portentious decisions in the absence of adequate scientific data; such essentially non-scientific judgments cannot fairly be left to industry or the research community, which have an understandable tendency to favor experimentation and the application of scientific findings. A more democratic decision-making mechanism is needed. It is urgent that a legal framework for public control of the technological applications of recombinant DNA be set up without delay, for industrial activity is underway and applications are imminent. Experience in other branches of technology indicates that controls will someday be necessary; in fairness to both industry and the public, we should not wait until the need is palpable before instituting procedures that may avoid future disasters. Preoccupation with guidelines for academic research should not be allowed to divert attention from the more serious aspects of the recombinant DNA problem.

Yours sincerely,

Liebe F. Cavalieri, Ph. D.
Member, Sloan-Kettering Institute
Professor of Biochemistry, Cornell
University Graduate School of Medical
Sciences

Barbara H. Rosenberg, Ph.D.
Associate Member, Sloan-Kettering Institute
Associate Professor of Biochemistry, Cornell
University Graduate School of Medical
Sciences

LFC:BHR:mb

AREA CODE 608
PHONE 262-2177

MEDICAL CENTER

McARDLE LABORATORY
FOR CANCER RESEARCH

UNIVERSITY OF WISCONSIN • MADISON, WISCONSIN 53706

February 1, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, MD 20014

Dear Doctor Fredrickson:

Thank you for your kind letter of January 16, 1978 pertaining to the proposed revisions of the N.I.H. Guidelines.

I would like to emphasize again the urgency of instituting a prompt change in the Guidelines that would permit immediate exclusion from under the M.U.A. requirements of all experiments on recombining genes of E. coli K-12, its phages and plasmids (intraspecific E. coli K-12 cloning). There was uniform agreement among the members of your Advisory Committee as to this change, and even Bob Sinsheimer advocated it. I am sure that you could do so by a simple official announcement.

The damage being done by the regulations based on the Guidelines and the ensuing bureaucracy is tremendous. Many scientists waste time, effort and taxpayers' money by trying to do research without applying the recombinant DNA technique, just because they do not want to be drawn into the bureaucratic mire. Merely to get simple permission to clone E. coli or λ phage DNA in an E. coli plasmid takes several months, piles of paper and hours and hours of wasted time and effort. Also, your Office of Recombinant DNA and the local Biosafety Committees are overburdened.

I shall try to telephone you early in February to learn whether you will exclude early this Spring the intraspecific E. coli K-12 cloning from the bureaucratic requirements of the M.U.A.'s. I realize that any of your decisions could be criticized either as "bureaucratic delay" and "foot dragging" or as "unnecessary haste". Thus, the selective policy of (1) rapid approval of uncontested changes and (2) careful consideration and somewhat delayed approval of disputed aspects of the revised Guidelines appears to me to be the wisest course of action, combining the best of both alternatives and showing the flexibility and responsiveness of the administrative process and your courageous leadership.

With best personal regards,

Sincerely yours,

Waclaw Szybalski
Professor of Oncology

WS:ms

72 Jane Street
New York N Y 10014
(212) 675-7173

Coalition for Responsible Genetic Research

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Membership Secretary

Francine R. Simring
Executive Director

February 9, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Md. 20014

Dear Dr. Fredrickson:

At the last meeting of the Executive Committee of the Coalition for Responsible Genetic Research, the attached comment on the proposed revisions to the NIH guidelines was approved. We are sending it to you for your due consideration on further actions concerning the proposal.

We are confident that the NIH will adhere to the procedural and scientific standards which the public expects.

Very truly yours,

Francine Robinson Simring

FRS:fh

Francine Robinson Simring
Executive Director

COMMENT ON THE PROPOSED REVISED

GUIDELINES FOR RECOMBINANT DNA RESEARCH

Periodic updating and reconsideration of the NIH Guidelines for Recombinant DNA Research is a necessary activity of which the Coalition for Responsible Genetic Research approves. However, the manner in which the current proposal for revisions has taken place is not satisfactory. A serious omission in the process has been the failure to obtain the input of relevant scientific disciplines, such as pollution biologists, microbial ecologists, and epidemiologists, in the consideration of the revisions. Although the December 15-16, 1977 public meeting at NIH was a positive step, it should have been held before the revisions were drafted, as a means of developing needed information. Furthermore, an opportunity for effective public participation has not been provided for by the NIH. Nor was an environmental impact statement prepared on the revisions as required by law.

The Coalition for Responsible Genetic Research is opposed to relaxation of the NIH Guidelines at this time for the following reasons:

(1) There is insufficient scientific evidence to warrant relaxation;

(2) Unpublished research has been used as a basis for the proposed revised Guidelines in violation of classical scientific canon;

(3) A systematic risk assessment program has not been conducted in order to determine the levels of hazard;

(4) The procedures by which the Guidelines are being revised are inadequate.

Further action on relaxation of the NIH Guidelines should be suspended until these defects are remedied.

Concerning Roles and Responsiblities: we feel that in order to protect against the influence of competitive pressures, the biohazard safety officer should not be involved in biological research, but should have as his sole responsibility the control of biologic hazards. Also, there should be substantial representation on the biohazards safety committee of laboratory support personnel and members of the local community. These requirements should be extended to all institutions regardless of the P level of recombinant DNA work being performed there.

We are especially concerned that the proposed revised Guidelines contain provisions for exemptions from the list of prohibited experiments and for exemption from limits on culture volume. We feel that it is premature to contemplate such exemption before systematic risk assessment has taken place. Further, since the NIH is promoting this technology, we do not feel that it can take an appropriately neutral stance in judging operations that will affect the entire society. Some other body, not involved in the promotion of recombinant DNA activities,should be responsible for review and assessment of all application for exemption. In addition, there should be a provision for formal public review of all exemptions to the Guidelines and compliance with the National Environmental Policy Act with respect to such exemptions.

Iowa State University of Science and Technology Ames, Iowa 50011

Department of Genetics
8 Curtiss Hall

Telephone: 515-294-3908

February 10, 1978

Dr. Donald Fredrickson
N.I.H.
9000 Rockville Place
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I have been in communication with Dr. William Garland and others on the Advisory Committee on DNA Regulation regarding containment facilities necessary for certain proposed recombinant DNA experiments. I have been told by all I have contacted that the Guidelines, even the recently revised version, do not mention the type of experiment we propose and thus give us no indication of the facilities needed. Dr. Garland suggested I write to you pointing out this gap in the Guidelines in the hope that some thought might be given to the problem before the Committee meets again in April.

The experiment in question is one involving the isolation and purification of messenger RNA's involved in the fixation of nitrogen by Azotobacter vinelandii (a non-pathogenic, free living, aerobic bacterium). The use of reverse transcriptase is proposed to form the DNA copy, and DNA polymerase to restore double stranded structure. This piece of DNA would then be spliced into the mitochondrial DNA isolated from either Chlamydomonas reinhardii or Solanum tuberosum (potato). Chlamydomonas is a non-pathogenic, free living, single-celled, green alga, and the mutant we should be using grows only as protoplasts.

Once spliced into the mitochondrial DNA the DNA would be reintroduced into isolated mitochondria which would in turn be reintroduced into their respective protoplasts. Growth would be maintained on nitrogen-deficient media and nitrogen fixation activity assayed by acetylene reduction activity.

Our present facilities rate as P2 and could with but small inconvenience be transformed into P3. We wish to write up this proposal as soon as possible

and would very much appreciate the hole in the guidelines being filled so that we may indicate the facilities necessary in that proposal.

I look forward to hearing from you and the Committee as soon as possible.

Very sincerely,

Kenneth L. Giles
Associate Professor

KLG/mj

COLLEGE OF ARTS & SCIENCES

NEW YORK STATE
COLLEGE OF AGRICULTURE AND LIFE SCIENCES
A Statutory College of the State University

CORNELL UNIVERSITY
DIVISION OF BIOLOGICAL SCIENCES
ITHACA, N.Y. 14853

SECTION OF BOTANY, GENETICS & DEVELOPMENT
PLANT SCIENCE BUILDING

February 13, 1978

Dr. Donald Fredrickson
Director, N.I.H.
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing concerning an important problem which has resulted from current N.I.H. procedures with respect to recombinant DNA. The only hosts permitted at this time for the cloning of hybrid DNA molecules are Escherichia coli K12 and animal cells. A recent advance in my own laboratory has made it possible to transform baker's yeast (Saccharomyces cerevisiae) with hybrid plasmids and therefore to insert virtually any foreign DNA molecule into the genome of this organism. Baker's yeast is not pathogenic in any mammal, does not exchange DNA with any pathogens, and has no DNA viruses. The sophisticated biochemistry and genetics of yeast together with the technology offered by our new finding makes baker's yeast ideal as a safe, efficient cloning host. Scientists are not permitted to develop this system because of the strict interpretation of the Guidelines by the Office of Recombinant DNA. I would like to point out that this interpretation is hindering science in our country, placing many scientists at a disadvantage, causing confusion to the informed citizen, and reducing faith in the wisdom and ability of the N.I.H. to administer the guidelines. The work has been sanctioned by the National Science Foundation and the American Cancer Society so that scientists with support from these agencies can proceed into this fruitful area while their colleagues with N.I.H. support cannot. Clearly, this contradiction in interpretations by national funding agencies gives those of us with support from non-N.I.H. sources as well as foreign scientists an unfair advantage. Local recombinant DNA committees in San Diego, Ithaca, Cambridge, and Stanford have given overwhelming endorsement of experiments using yeast as a host. They recognize, as our own local committee did, that "any rational observer would agree that baker's yeast is safer than E. coli". All newspaper accounts emphasize that "there does not appear to be any way in which experimentally altered yeast could become a health hazard" (Christian Science Monitor, Jan. 11, 1978). Therefore, the current practices of the N.I.H. not only are at variance with those of other national funding agencies, but also with the judgment of local academic committees and informed public opinion.

I would urge you to permit the use of baker's yeast as a host for recombinant DNA. In making this request I am not asking for exceptions to the N.I.H. Guidelines. In fact, to permit the use of yeast as a host would be fully consistent with these guidelines which urge: "Thus, while proceeding cautiously with E. coli, serious efforts should be made toward developing alternate host-vector systems; ...". Yeast is an ideal alternate host system. On pg. 27920, under (c) at the top, the level of containment for fungal or similar lower eucaryotic host-vector systems is given. "We therefore consider that the containment guidelines given for experiments with E. coli K12 and other procaryotic host-vectors (Section III B-1 and -2 respectively) provide adequate direction for experiments with those lower eucaryotic host-vectors". In effect, allowing the use of yeast as a host would be a more liberal interpretation of a portion of the guidelines which is somewhat ambiguous. This more liberal interpretation would remove the inequalities of the current situation and permit the development of a safer cloning host. I believe that such an action would restore confidence in the N.I.H. and its ability to oversee the development of recombinant DNA technology in our country.

Sincerely,

Gerald R. Fink

Gerald R. Fink
Professor of Genetics

GRF:fo

DEPARTMENT OF MICROBIOLOGY
THE MEDICAL COLLEGE OF WISCONSIN
561 NORTH FIFTEENTH STREET
MILWAUKEE, WISCONSIN 53233
(414) 272-5450

17 February 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Re: Transformation of yeast cells with recombinant DNA.

Dear Dr. Fredrickson,

Due to the recent announcement from Dr. Gerald Fink that yeast may be successfully transformed with yeast-*E. coli* hybrid DNA plasmids, I respectfully request that this new host-vector system be approved by NIH.

The reasons for approving such a new host-vector system are many:

1) The yeast system is safer than *E. coli* since *Saccharomyces* is not a commensal of man,

2) Since NSF consents to the yeast host-vector system, grantees from NIH are put at a distinct disadvantage in being deprived of this system, and

3) The yeast system offers the first demonstrable eucaryotic system in which transformation works, thus availing a more apt cell in which to study eucaryotic regulation.

I write unbiased since I am not currently an NIH grant recipient (although I will submit a grant proposal in the near future). I realize NIH, and specifically the Office of Recombinant DNA Activities have been "under fire" for such frequent revision of the original *Recombinant DNA Guidelines*, however, this rapidly developing area deserves an equally rapidly developing political superstructure with which it can be regulated. In the present case, since less and not more danger is afforded the human community, I urge immediate attention to revision of the *Guidelines* in order to allow transformation of yeast cells with yeast-*E. coli* hybrid plasmid DNA.

Yours sincerely,

Bruce Molholt, Ph.D.
Assistant Professor

cc: Dr. Daphne Kamely
Office of Recombinant DNA Activities

COVINGTON & BURLING
888 SIXTEENTH STREET, N.W.
WASHINGTON, D.C. 20006

TELEPHONE (202) 452-6000

WRITER'S DIRECT DIAL NUMBER

HOWARD C. WESTWOOD
JOHN T. SAPIENZA
JAMES H. McGLOTHLIN
ERNEST W. JENNES
STANLEY L. TEMKO
DON V. HARRIS, JR.
WILLIAM STANLEY, JR.
WEAVER W. DUNNAN
EDWIN M. ZIMMERMAN
JEROME ACKERMAN
HENRY P. SAILER
JOHN H. SCHAFER
ALFRED H. MOSES
JOHN LeMOYNE ELLICOTT
PAUL R. DUKE
PHILIP R. STANSBURY
CHARLES A. MILLER
RICHARD A. BRADY
ROBERT E. O'MALLEY
EUGENE I. LAMBERT
JOHN VANDERSTAR
NEWMAN T. HALVORSON, JR.
HARVEY M. APPLEBAUM
MICHAEL S. HORNE
JONATHAN D. BLAKE
CHARLES E. BUFFON
ROBERT N. SAYLER
E. EDWARD BRUCE
DAVID N. BROWN
PAUL J. TAGLIABUE
ANDREW W. SINGER
DAVID H. HICKMAN
RUSSELL H. CARPENTER, JR.
NICHOLAS W. FELS
THEODORE L. GARRETT
DANA T. ACKERLY
JOHN M. VINE

CHARLES A. HORSKY
W. CROSBY ROPER, JR.
DANIEL M. GRIBBON
HARRY L. SHNIDERMAN
EDWIN S. COHEN
JAMES C. McKAY
JOHN W. DOUGLAS
HAMILTON CAROTHERS
J. RANDOLPH WILSON
ROBERTS B. OWEN
EDGAR F. CZARRA, JR.
WILLIAM H. ALLEN
DAVID B. ISBELL
JOHN B. JONES, JR.
H. EDWARD DUNKELBERGER, JR.
BRICE McADOO CLAGETT
JOHN S. KOCH
PETER BARTON HUTT
HERBERT DYM
CYRIL V. SMITH, JR.
MARK A. WEISS
HARRIS WEINSTEIN
JOHN B. DENNISTON
PETER J. NICKLES
MICHAEL BOUDIN
BINGHAM B. LEVERICH
ALLAN J. TOPOL
VIRGINIA G. WATKIN
RICHARD D. COPAKEN
CHARLES LISTER
PETER D. TROOBOFF
WESLEY S. WILLIAMS, JR.
DORIS D. BLAZEK
WILLIAM D. IVERSON
S. WILLIAM LIVINGSTON, JR.
JAMES R. ATWOOD
COLEMAN S. HICKS

NEWELL W. ELLISON
JOHN G. LAYLIN
H. THOMAS AUSTERN
FONTAINE C. BRADLEY
EDWARD BURLING, JR.
J. HARRY COVINGTON
COUNSEL

JOHN SHERMAN COOPER
OF COUNSEL

TWX: 710 822-0005
TELEX: 89-593
CABLE: COVLING

March 3, 1978

Donald S. Fredrickson, M.D.
Director
National Institutes of Health
Building 1, Room 124
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Don:

This letter is an unfortunately delayed response to your request that each of the individuals who comprised the Advisory Committee which met with you on December 15-16, 1977, to consider the proposed revisions of the current Guidelines for research on recombinant DNA molecules, furnish you with specific conclusions and recommendations. The following comments will expand upon my remarks at the end of the meeting.

I

As happened at the February 1976 meeting when the current Guidelines were being considered, the basic issue whether there should be any research on recombinant DNA molecules, and if so under what conditions, was clearly raised. Dr. Schwartz argued that all such research should be banned (by placing all of it under P4 restrictions) and Dr. Watson argued that the scientific community should be given total freedom to engage in such research (by eliminating the present biological and physical containment measures and by revoking the current list of prohibited experiments). Neither of these positions appeared to me to be persuasive, in light of all of the other information presented at the meeting.

As I stated during the February 1976 meeting and in my subsequent letter to you of February 20, 1976, the burden of demonstrating to the satisfaction of the public that research on recombinant DNA molecules is "safe" (i.e., that the level of risk is both reduced as far as is reasonably feasible under the circumstances and does not outweigh the potential benefits) rests on those who wish to proceed with this research. This is the public policy position adopted by Congress with respect to other comparable human endeavor. A person who wishes to expose a human being to an experimental new drug or food additive, or who wishes to bring into commercial production a new chemical substance for any use whatever, bears the burden of both informing the government of that intention and of submitting sufficient information to persuade the government agencies involved that the new substance, under the proposed conditions of use, has been shown by adequate data to be safe enough to proceed with the course of action proposed. It is important to note that this public policy is not based upon knowledge, or even apprehension, that the proposed action will be unsafe. Rather, it is based upon the public policy determination that no new substance can be presumed to be safe, and thus that those who wish to proceed with any particular new substance must first satisfy their burden of demonstrating safety. This is in contrast with the public policy that previously prevailed, under which manufacturers of products of this nature were free to market them without first demonstrating safety. In the past few years, the public has very deliberately rejected the old policy under which new substances were presumed to be safe until proven otherwise, and has adopted a new policy under which substances are presumed not to be safe until they are shown to be safe.

The current public policy is thus not a statement of scientific fact, but rather is a statement of public policy emanating from scientific uncertainty. It embodies a conclusion that neither specific humans nor the environment should be exposed to new substances until their safety has adequately been evaluated. It is not, and could not be, a determination that all new substances are unsafe.

I emphasize the conceptual basis for this public policy because many of the comments made at the December 1977 meeting appeared seriously to misperceive it. The original wisdom of the moratorium is not denigrated by subsequent new thought and information revealing that some of the initial concerns about this type of research are misplaced, any more

than the initial caution in use of an experimental new drug is made foolish by subsequent thought and information demonstrating that it is a safe and effective therapy. Public policy dictates caution in the face of scientific uncertainty, particularly when faced with the possibility of consequences, however remote they may be, that could have enormous public impact. I have heard no one suggest, for example, that all of the elaborate precautions taken upon the return from the first moon exploration, to assure that no virulent organisms would be brought back, were a foolish and wasteful extravagance, in light of our present knowledge that they were totally unnecessary.

In summary, the public policy issue is not, and never has been, whether there is either evidence or even a well-founded apprehension that research on recombinant DNA molecules is dangerous. Rather, the issue is one of proceeding gradually, on the basis of accumulating knowledge and experience which provides ever greater assurance of safety, in order to satisfy the public that there are no unreasonable risks involved.

II

Throughout the meeting, and indeed in all of the discussion I read and hear about this research, there appears to be enormous confusion about the type of "risk" that must be considered in evaluating the propriety of research on recombinant DNA molecules. It appears to me that there are four risks involved (one of which is simply another way of looking at the benefits to be derived from this research).

First, there is the risk to an individual laboratory worker. Such risks occur frequently in all types of scientific research. If this were the only risk involved, it might well be handled simply by obtaining the informed consent of all those exposed to the risk in the laboratory. Certainly, public concern about this type of very narrow risk would be far less than about risks that are potentially of broader applicability to the public at large.

Second, there is the theoretical risk of unleashing a new form of pathogen that would result in an epidemic of significant public magnitude. This type of risk, quite obviously, cannot be handled by informed consent. It is

basically this type of theoretical risk that has been used to justify the relatively stringent control over recombinant DNA molecule research, as contrasted with other basic research that has gone unregulated in the past. It is important that consideration of this risk be kept entirely separate and distinct from the risk to an individual laboratory worker, and that the two not be confused.

Third, there is the risk that information gained from research on recombinant DNA molecules may ultimately be misused as, for example, a tool of war or terrorism. It is impossible to quantify or analyze objectively this risk. There is little scientific and technological research today that cannot theoretically be misused; certainly, people have succeeded in misusing a great deal of the most important scientific and technological advancements of our society in the past. I therefore find it impossible to base any public policy with respect to scientific research on the utterly conjectural contention that it could, in some way, potentially be misused in the future. Any public policy based on that premise would require that we disengage from all scientific and technological endeavor and indeed expunge much of what we have learned in the past. Thus, this form of risk is not, in my judgment, worthy of further consideration.

Fourth, there are the many risks to individuals and to society as a whole from not proceeding with this research. To the extent that significant benefits can be projected, both directly from new products that can be produced and indirectly from the new information that can be gained, we will all suffer harm if the research is unnecessarily or unduly restricted or even prohibited. Lawyers are taught that the failure to act can be as culpable as direct action. The moral and ethical concerns, and risk to health, of the failure to pursue this very fruitful avenue of research must therefore also be considered in a far more detailed way than has been done to date.

At the meeting, Dr. Schwartz criticized the risk analysis that has been conducted to date on research on recombinant DNA molecules. When asked at the meeting to provide his own assessment of the risk, however, he was unable to do so. The materials he provided for the record, moreover, simply criticized the risk assessment of others without offering his own risk assessment. Indeed, they question

whether any risk assessment is possible. It is, of course, relatively easy to criticize any form of risk assessment, since this is a fairly new field and there are inherent uncertainties in analyzing a still-emerging area of research like recombinant DNA. I am not satisfied, however, with his suggestion that risk assessment in this area may well not be feasible. Even if definitive answers cannot be obtained, we must do the best that we can at this time. It is simply unacceptable to contend that, since definitive risk assessment is not feasible, all research on recombinant DNA molecules should cease; this would mean that the research needed to engage in more definitive risk assessment would itself be precluded. If Dr. Schwartz's approach were applied to all human endeavor, the progress of civilization would be substantially impeded if not halted for fear of unknown risks.

The difficulty of risk assessment in this area is, on the other hand, one reason for continuing the policy of proceeding with caution on research with recombinant DNA molecules. As more becomes known, risk assessment will become less speculative and more reliable.

III

In general, I believe the process has been working exactly as one would have hoped. Faced with the realization that they carry the burden of showing to society that research on recombinant DNA molecules can be conducted without unreasonable risk, scientists have responded in their finest tradition. They have undertaken substantial research and analysis to demonstrate that the risk is small and that the potential benefits outweigh that risk. Those immediately involved in laboratory experimentation on recombinant DNA molecules have enlisted other scientists who can bring relevant data and information to bear on this matter. The result has been the development of a great deal more information bearing on the risks of this type of research than was available, for example, at the time of the February 1976 meeting.

From all of the information made available at the December 1977 meeting, I continue to concur that the potential benefits of research on recombinant DNA molecules outweigh the risks of this research. As you know, I supported the general thrust of the original draft Guidelines, while

raising in my letter of February 20, 1976 specific questions and suggestions for modification. I felt that your response to the suggestions that I and others made about the draft Guidelines at that time were fully and fairly covered in your preamble to the final Guidelines.

In my judgment, the data and information accumulated since the final Guidelines were promulgated, and which were made available at the December 1977 meeting, support the modifications of the Guidelines that you have now proposed, although I again set out in this letter some specific questions and comments for your consideration. I agree that there is both scientific evidence and a growing scientific concensus that this type of research can reasonably be pursued with greater assurance of safety than scientists once thought, and that some experiments can now be exempted from the Guidelines and others can be reclassified to lower physical or biological containment levels. I also anticipate that, as further evidence of safety is obtained, still further loosening of restrictions will be permissible in the future. This is, of course, an on-going process which can never be allowed to remain static.

IV

Regrettably, however, the procedure that has been followed in pursuing these modifications of the Guidelines has been inadequate. The preamble to the proposed revision of the Guidelines published in the Federal Register of September 27, 1977 (42 F.R. 49596) is short to the point of being wholly uninformative. It contains neither the helpful background information distributed at the December 1977 meeting nor any of the other unpublished or published scientific data and information to which reference was made at that meeting as the basis for the judgment that increasing evidence of safety justifies modification of the Guidelines.

A proper preamble would specify each proposed revision of the Guidelines, explain the impact of those proposed revisions, state why there is less concern about potential risk now than there was when the Guidelines were promulgated, provide the published and unpublished data and information on the basis of which that determination has been made, and thus contain a thorough explanation of the decisional process. This would provide a basis on which both scientists and the general public could understand the reasons for the proposal and submit appropriate comment.

Particular reference was made, at the December 1977 meeting, to the Falmouth Conference (attendance at which was by invitation only) and unpublished scientific data that are not yet generally available. It is apparent that you place strong reliance upon both the unpublished data and the conclusions of the Falmouth Conference in proposing the revisions of the Guidelines as published in the Federal Register of September 27, 1977. Yet none of this data and information was referred to explicitly in the preamble to the proposal, and none of it was made available to the public for review in connection with this matter.

Whether or not one regards the Guidelines legally as "regulations," and thus as subject to the procedural requirements of the Administrative Procedure Act, it is apparent that the procedure that has been utilized to propose these revisions in the Guidelines is seriously flawed. I need not rehearse the two-year history of intense public interest in these Guidelines. It is simply not tenable now to propose modifications that would exempt some experiments from the Guidelines, and reduce the level of control over others, without specifying, discussing in some detail, and making public the scientific basis for those modifications. By attempting to short-cut this process, NIH has unfortunately acted in unseemly and unnecessary haste, and has given an impression that can only intensify the concern and suspicion of those who believe that inadequate controls exist for this type of research.

In order to remedy this situation, I would recommend that the proposal published in the Federal Register of September 27, 1977 be republished as a new proposal, with an adequate preamble fully explaining all of the revisions and the reasons for them. All of the unpublished scientific data and information supporting the proposal, including a full transcript of the Falmouth Conference, should be placed on the public record for inspection and comment, and its availability should specifically be mentioned in the preamble.

Of course, adequate time must again be given for public comment on this proposal. I suggested at the December 1977 meeting that 30 days might be a sufficient time for additional comment. In view of the fact that the unpublished data and the transcript of the Falmouth Conference have not yet been made public, however, I would suggest that this time period for comment be 60 days rather than 30 days.

V

As stated in my letter of February 20, 1976, these Guidelines should properly be regarded as "regulations," which impose substantive obligations upon researchers working pursuant to NIH grants and contracts. In that letter I said that "No one should be misled into believing that they will not be rigidly and completely enforced, through the grant and denial of NIH funds." I also pointed out that, from a legal standpoint, "there is a substantial possibility that a court would determine that these guidelines may not be enforced by NIH even for funding purposes unless they are proposed for comment and adopted through publication in the Federal Register."

Some of the concerns that I perceived at that time are now becoming far more troublesome. By persisting in calling these "Guidelines," it appears that some people may be misled into believing that in fact they will not be rigidly and completely enforced. One can hardly blame researchers from taking this document at face value, i.e., by interpreting them to be merely "Guidelines" and not be be legally binding regulations. I find it difficult, as others must, to reconcile your statements that these are mere "Guidelines" with your statements that all NIH-supported researchers must comply with them.

I therefore believe that it is time to stop this pretense. Calling them "Guidelines" has done far more harm than good. They should, in my judgment, forthrightly be proposed and promulgated as formal binding regulations on the basis of which NIH funds will be granted or denied, and with which all NIH-supported research must comply.

In February 1976 I recommended that these requirements be promulgated as legally binding upon all research on recombinant DNA molecules in this country pursuant to Section 361 of the Public Health Service Act, 42 U.S.C. 264, and I reiterated that viewpoint at the December 1977 meeting. You stated, at that time, that the Interim Report of the Federal Interagency Committee on Recombinant DNA Research, dated March 15, 1977, was not sanguine about the use of Section 361. The wording of that Report (at page 35) is as follows:

> "Both DOT and CDC, in implementing the HMTA and section 361 with respect to biological products, have essentially aimed just at imposing labeling, packaging, and shipping requirements. This approach is in line with the statutory language which emphasizes movement. Section 361 could perhaps be interpreted more broadly to serve as legal support for more comprehensive regulation. However, in order to do so there would presumably have to be a reasonable basis for concluding that the products of all recombinant DNA research cause or may cause human disease. Such a conclusion would undoubtedly be tenuous at best, and it is unlikely that resulting requirements could be effectively imposed and enforced."

This is the sole analysis of Section 361 in that entire report.

Since the December 1977 meeting, I have had occasion to investigate the legal aspects of Section 361 further. Enclosed is a letter I prepared for Dr. Gilbert S. Omenn of the Office of Science and Technology Policy on this subject. Suffice it to say that, in my judgment, Section 361 is legally available for use in governing all research on recombinant DNA molecules if, as a matter of policy, the Department of HEW concludes that it should be so used. The decision whether to use Section 361 for this purpose is, of course, a policy decision, not a legal decision.

Of course, the use of Section 361 would be obviated by enactment of legislation currently being considered by Congress. If that legislation is not enacted and the Department of HEW declines to assert jurisdiction under Section 361, however, a serious regulatory void will exist. It is likely, under these circumstances, that the Occupational Protection Agency will be forced to exert jurisdiction under other regulatory statutes. This would, in my judgment, be a serious error. NIH obviously has the expertise in this matter and should not surrender its role as the lead agency. If the Department of HEW does default on its responsibilities, however, other regulatory agencies will have no alternative

but to take appropriate action. In short, it is imperative that the Department of HEW continue to exercise some initiative in pursuing adequate regulation (but not over-regulation) of all research on recombinant DNA molecules in the United States, either through existing or pending legislation, in order to reassure the American public that its interests are fully protected and to forestall other regulatory controls that could seriously hinder the future of reasonable scientific progress in this highly important experimental area.

VI

During the course of the two days of discussion at the December 1977 meeting, a number of substantive and procedural provisions of the Guidelines were discussed which appear to deserve further consideration.

A. Substantive issues.

At the outset, I should point out that I do not concur with those who objected to the wording of the Guidelines as "vague." Having spent 4 years in the government attempting to fashion detailed regulations governing complex and sensitive scientific issues, I understand quite fully the limitations of the process. Vagueness is an inherent problem in any regulation. My review of the Guidelines does not indicate that they are "vaguer" than comparable regulations in other equally complex areas. Thus, my comments relate to specific aspects of the Guidelines and not to any general deficiency.

1. As published in the Federal Register of September 27, 1977, it was proposed that present Appendix D (which sets forth supplementary information on physical containment) would be deleted. Apparently, anticipating concern about this proposed deletion, it was stated during the December 1977 meeting that NIH is reconsidering that proposed deletion.

I would strongly urge that Appendix D be retained. To the extent that questions have been raised about specific aspects of that Appendix, they should be resolved by further modification of those provisions. But it is extremely important, in my opinion, to retain an appendix that provides at least general guidance about adequate provisions for physical containment.

I pointed out in my letter of February 20, 1976, the importance of specifying the intended requirements for physical containment. The experience of the Food and Drug Administration in monitoring "good laboratory practices" in the intervening two years underscores this point. FDA has discovered that industrial research laboratories maintain the best laboratory practices, contract laboratories are the second best, and academic laboratories are worst. In the face of this evidence and a growing concern by all regulatory agencies about the need to establish guidelines for good laboratory practices, I believe it would be a serious mistake to eliminate Appendix D.

2. Mere inclusion of Appendix D, moreover, would seem inadequate to assure that adequate physical containment is in fact achieved. The suggestion made at the December 1977 meeting that the Guidelines be revised to require specific training programs with respect to physical containment practices seems sensible.

3. It became apparent at the December 1977 meeting that, even if the Guidelines are not promulgated as regulations governing all research on recombinant DNA molecules in the United States, they should be revised to permit the voluntary participation of industry and of other researchers who are not receiving funds from NIH or otherwise from the Federal government. Representatives of industry stated that they are presently complying with the Guidelines and would appreciate the opportunity to participate under them, on a voluntary basis, in full partnership with NIH. Revision of the Guidelines to reflect such voluntary participation would, in itself, do much to reassure the public that inappropriate research on recombinant DNA molecules is not being conducted.

The only concern expressed at the meeting by the representatives of industry related to the need to protect trade secrets. As I stated at the meeting, this should present no problem whatever. As Part VIII of the enclosed letter to Dr. Omenn states, an existing Federal statute, 18 U.S.C. 1905, explicitly provides that trade secret information provided to the government may not be released to the public by any government employee under pain of criminal penalty. The Interim Report of the Federal Interagency Committee on Recombinant DNA Research, dated March 15, 1977,

similarly concludes (at pages 36-37) that this statutory provision would provide adequate protection against public disclosure of any confidential business information. Numerous other government agencies daily receive confidential commercial information, and retain it as confidential without public disclosure, pursuant to 18 U.S.C. 1905 and other similar confidentiality provisions of the law. Thus, there is no reason why NIH should hesitate to amend the Guidelines to provide for full participation of industry and other researchers, with adequate protection for all confidential and trade secret information that might be furnished to NIH as a result.

4. It is important that the Guidelines assure adequate public representation on, and access to, the local biohazards committee. I believe that this can be accomplished without sacrificing the confidentiality needed to protect valid trade secret and commercial information. Disclosure to a biohazards committee, which includes lay persons from the community, is uniformly regarded as not destroying the confidentiality of the information disclosed. Those portions of a meeting dealing specifically with confidential information can, of course, be closed to the general public. Portions of the meetings dealing with broad safety and other policy issues, on the other hand, can be opened without fear of disclosing confidential information. This distinction is uniformly followed by all Federal advisory committees under the Federal Advisory Committee Act today, without serious difficulty.

Thus, the Guidelines should specify that public notice is required for all meetings of the biohazards committee, giving the time, place, and agenda for the meeting. The notice should also specify what portions of the meeting will be open and closed and, if possible, state that the open portions will be held first. These requirements are now applicable to all Federal advisory committees.

Finally, public notice should be given whenever a vacancy exists on a biohazards committee, so that interested persons can submit nominations for persons to be considered for the vacancy. Those nominations should not be binding, and the ultimate composition of the biohazards committee should be chosen in a way that reflects adequate balance and expertise. Nonetheless, public participation in the

nomination process will further enhance the public perception of these committees as truly representing and protecting the public interest. Many government agencies follow this nomination procedure for Federal advisory committees today.

In general, present FDA regulations governing advisory committees, in 21 C.F.R. Part 14, could be used as a model for the provisions in the Guidelines governing local biohazards committees.

5. The Guidelines presently do not include provisions relating to inspection in order to assure compliance of research conducted with NIH funds with the requirements of the Guidelines. The Guidelines should make clear that NIH representatives or other employees of the Department of HEW may, at any time, upon a proper showing of credentials, inspect any NIH-funded research on recombinant DNA molecules to assure that it is being conducted in accordance with the Guidelines. Once again, this will create greater public confidence that the Guidelines are not just paper provisions but in fact are being enforced with adequate inspection.

6. In order to emphasize that the Guidelines will in fact be enforced, specific penalties should be stated. The Guidelines should make clear that non-compliance with the Guidelines may result in termination of the grant and, depending upon the circumstances, termination of other NIH research grants involving the investigator and the institution. The specific penalty will, of course, depend upon all the facts of the situation. Deliberate violation of the Guidelines by an investigator or by an institution should, however, clearly be stated to be a serious offense that will carry with it serious penalties.

7. During the December 1977 meeting, it was charged that one private company had financed research on recombinant DNA molecules at one or more private university laboratories not in compliance with the Guidelines. Subsequently, it was learned that this has not in fact happened, and that the company and the institutions do not intend to undertake any research that is not in compliance with the Guidelines.

The question arises, nonetheless, whether the Guidelines could be revised to broaden their reach. Although I have not undertaken any legal research on the matter, it

appears to me within the NIH authority to require that all research on recombinant DNA molecules conducted in any institution that receives any NIH money whatever must, as a condition for receiving any NIH money (including money used for purposes other than research on recombinant DNA molecules), be in compliance with the Guidelines. This would mean that no institution which undertakes any research on recombinant DNA molecules could obtain any money for any purpose whatever from NIH without agreeing to follow the Guidelines, even if the research on recombinant DNA molecules itself was financed from non-government sources. Since both industry and other private research organizations have stated that they intend fully to comply with the Guidelines with respect to all research on recombinant DNA molecules, such a provision would work no hardship whatever and would have the salutary benefit of reassuring the public on this matter.

8. There appeared to be a scientific consensus at the December 1977 meeting about the need for greater flexibility to permit experimentation on animal viruses. I obviously am not qualified to offer any judgment on this issue. The public and scientific concern about SV-40 virus which I expressed in my letter of February 20, 1976, leads me to suggest that some care must be taken in differentiating between different animal viruses. Although classification of this experimentation in P4 should not be done for "political" reasons, the depth of prior public concern about this matter because of the charge that the SV-40 contamination of polio vaccine did in fact result in harmful effects in children requires, in my opinion, substantial scientific discussion and justification before reclassification of that particular experimentation to P3 is undertaken. Ultimately, scientific judgment rather than "political" considerations must prevail, but quite clearly the "political" concerns must be taken into account in determining the extent and depth of scientific justification needed before reclassification can be achieved.

B. Procedural Issues.

The Guidelines exhibit remarkable scientific ingenuity. This undoubtedly reflects the extraordinary knowledge and background of the scientists who contributed to their development during the past few years.

Unfortunately, the regulatory or procedural aspects of the Guidelines do not meet the same high standards as the scientific aspects. From an administrative law standpoint, the Guidelines are pedestrian and, indeed, defective. The procedures embodied in the Guidelines simply do not reflect adequate attention to elemental concepts of due process of law. This is understandable, since they were developed by scientists rather than by experts in administrative law.

I have identified the following 7 areas where specific procedures are needed and where the Guidelines presently set forth no applicable procedures whatever:

1. Development, promulgation and amendment of a list of non-novel experiments.

2. Exemptions for specific experiments or classes of experiments from the requirements of the Guidelines (e.g., risk assessment experiments).

3. Future changes in the physical or biological containment classification for particular experiments.

4. Certification of host-vector systems.

5. Large volume exceptions.

6. Nomination and selection of members of the Recombinant Advisory Committee (RAC).

7. Future modification of the Guidelines.

In each of these areas, a variety of models exist from which to develop fair administrative procedures. Without procedures, NIH, the scientific community, and the public at large simply will be unable to understand how the various provisions in the Guidelines will be implemented. It is impossible to determine, for example, how one applies for certification of a new host-vector system, what procedure is applied by RAC in reviewing such an application, how the decision is announced, and other similar procedural details. As a result, it was stated during the December 1977 meeting that the public agenda of the RAC meeting during which certification of the EK2 system was considered did not even mention that this matter was on the agenda.

It is beyond the scope of this letter to suggest specific procedures for any of the above-listed areas. Some general comments on procedures that will enhance the flexibility of the Guidelines, while assuring adequate public notice and participation, were contained in my letter of February 20, 1976. I would urge that persons who are experienced in developing regulatory control mechanisms of this type be consulted on this matter.

I must emphasize, as I did in my letter of February 20, 1976, that inclusion of specific procedures need not require that the Guidelines become more stringent or inflexible. Indeed, the use of specific written procedures incorporated into the Guidelines can do much to eliminate the present rigidity of the Guidelines and assure greater flexibility in order more rapidly to respond to developing scientific knowledge. The concept of open and fair procedures, including public notice and participation, can readily be reconciled with the goal of administrative flexibility. Certainly, the idea of having an advisory committee of the type that was convened in February 1976 and December 1977 deliberate all changes in the Guidelines, or all exceptions and exemptions that are granted, would be unworkable. Unduly cumbersome administrative procedures of that type must be avoided at all costs.

Leaving these administrative procedures wholly up to the ad hoc judgment of NIH employees is far more likely to result in the type of confusion and clear errors that will generate enormous delay and inflexibility than are the inclusion of specific flexible procedures in the Guidelines themselves. This is best illustrated by the problem that you now face in repairing the procedural error caused by the inadequate preamble to the proposed modification of the Guidelines and the failure to make public the scientific basis for that proposal.

The procedural inadequacy of the Guidelines themselves stand in stark contrast to the extraordinarily careful and fair procedures you have employed in the February 1976 and December 1977 meetings held to provide a forum for public debate on the Guidelines. I have nothing but admiration for the way in which those two public meetings have been conducted. The steps taken to assure that all points of view have been adequately heard and considered have been nothing short of extraordinary. No person who has attended those

meetings has had anything less than a full opportunity to present views both orally and in writing. You have shown your full sensitivity to the concept of procedural due process in those meetings. That same sensitivity now needs to be reflected in specific procedural provisions in the Guidelines.

Serious questions were also raised about the adequacy of the environmental impact statement on the original Guidelines, which were not answered. Moreover, it appears that no draft environmental impact statement has yet been prepared for the proposed revision of the Guidelines. Greater care and attention should be paid to the requirements of the National Environmental Policy Act in order to assure the procedural integrity of the Guidelines.

VII

The discussion at the December 1977 meeting also revealed 4 areas that, in my judgment, deserve greater NIH priority even though they do not relate to any specific change in the provisions of the Guidelines at this time.

1. At present, it appears that scientists knowledgeable in the field are unable to develop objective criteria for classifying host-vector systems. As I have already stated, I am not surprised or troubled by the fact that some areas in the Guidelines require the use of subjective or vague terminology, reflecting the need for expert judgment. Nonetheless, NIH should take the lead in attempting to develop objective criteria that can be included in the Guidelines in the future.

2. It is evident that there are differences among scientists throughout the world with respect to the risks presented by various types of research on recombinant DNA molecules. The area of greatest evident dispute involves research on viruses, which is apparently permitted under P3 conditions in Europe but requires P4 conditions in the United States. NIH should actively pursue this matter on an International basis, to reconcile these differences. If the United States requirements are in fact too stringent, the full scientific justification for reclassifying these or other experiments should be made public and appropriate

changes in the Guidelines should then be promulgated. There should be no barrier whatever to appropriate reclassification of experiments, permitting less stringent physical or biological containment, as long as there is adequate scientific justification and full public disclosure and participation.

3. The development of new host-vector systems appears to be generally regarded as a very high priority. NIH should accordingly place significant emphasis in this area.

4. Perhaps because of the inherent difficulties of a risk assessment or a benefit/risk analysis, very little has been done in this area to date. NIH should, as one of its highest priorities, fund substantial work with respect to these matters in order more adequately to respond to the public concern about this type of experimentation.

5. It appeared from the discussion during the December 1977 meeting that NIH has not actively sought out researchers working on research on recombinant DNA molecules in private industry or in other institutions funded from non-government sources. I believe that this is a mistake, and that NIH should aggressively seek out these researchers and invite them to participate in the work of the Recombinant Advisory Committee and other related activities. This would cement the leadership of NIH in this entire area.

VIII

In conclusion, I wish to reiterate my general support both for the concept of the Guidelines and for the specific intention of the proposed modifications to reduce or eliminate current requirements wherever such reduction or elimination is scientifically justified. NIH was right when it concluded to issue the Guidelines, in order to reassure the public about the safety of this experimentation, and it is equally right in modifying the Guidelines to reflect new scientific information. Greater care must be taken in the future, however, to assure the procedural integrity of the Guidelines and to reflect due process of law in proposing and adopting amendments. I have enormous admiration for the great amount of work that NIH and outside scientists have put into this effort, and believe that it deserves the praise and support of the entire public.

Sincerely yours,

Peter Barton Hutt

PBH/mh
Enclosure

COVINGTON & BURLING
888 SIXTEENTH STREET, N.W.
WASHINGTON, D.C. 20006

TELEPHONE (202) 452-6000

WRITER'S DIRECT DIAL NUMBER

452-6300

TWX: 710 822-0005
TELEX: 89-593
CABLE: COVLING

HOWARD C. WESTWOOD
JOHN T. SAPIENZA
JAMES H. McGLOTHLIN
ERNEST W. JENNES
STANLEY L. TEMKO
DON V. HARRIS, JR.
WILLIAM STANLEY, JR.
WEAVER W. DUNNAN
EDWIN M. ZIMMERMAN
JEROME ACKERMAN
HENRY P. SAILER
JOHN H. SCHAFER
ALFRED H. MOSES
JOHN LEMOYNE ELLICOTT
PAUL R. DUKE
PHILIP R. STANSBURY
CHARLES A. MILLER
RICHARD A. BRADY
ROBERT E. O'MALLEY
EUGENE I. LAMBERT
JOHN VANDERSTAR
NEWMAN T. HALVORSON, JR.
HARVEY M. APPLEBAUM
MICHAEL S. HORNE
JONATHAN D. BLAKE
CHARLES E. BUFFON
ROBERT N. SAYLER
E. EDWARD BRUCE
DAVID N. BROWN
PAUL J. TAGLIABUE
ANDREW W. SINGER
DAVID M. HICKMAN
RUSSELL M. CARPENTER, JR.
NICHOLAS W. FELS
THEODORE L. GARRETT
DANA T. ACKERLY
JOHN M. VINE

CHARLES A. HORSKY
W. CROSBY ROPER, JR.
DANIEL M. GRIBBON
HARRY L. SHNIDERMAN
EDWIN S. COHEN
JAMES C. McKAY
JOHN W. DOUGLAS
HAMILTON CAROTHERS
J. RANDOLPH WILSON
ROBERTS B. OWEN
EDGAR F. CZARRA, JR.
WILLIAM H. ALLEN
DAVID B. ISBELL
JOHN B. JONES, JR.
H. EDWARD DUNKELBERGER, JR.
BRICE McADOO CLAGETT
JOHN S. KOCH
PETER BARTON HUTT
HERBERT DYM
CYRIL V. SMITH, JR.
MARK A. WEISS
HARRIS WEINSTEIN
JOHN B. DENNISTON
PETER J. NICKLES
MICHAEL BOUDIN
BINGHAM B. LEVERICH
ALLAN J. TOPOL
VIRGINIA G. WATKIN
RICHARD D. COPAKEN
CHARLES LISTER
PETER D. TROOBOFF
WESLEY S. WILLIAMS, JR.
DORIS D. BLAZEK
WILLIAM D. IVERSON
S. WILLIAM UVINGSTON, JR.
JAMES R. ATWOOD
COLEMAN S. HICKS

NEWELL W. ELLISON
JOHN G. LATLIN
H. THOMAS AUSTERN
FONTAINE C. BRADLEY
EDWARD BURLING, JR.
J. HARRY COVINGTON
COUNSEL

JOHN SHERMAN COOPER
OF COUNSEL

January 6, 1978

Gilbert S. Omenn, Ph.D., M.D.
Assistant Director for Human Resources
and Social and Economic Services
Office of Science and Technology
Policy
Washington, D. C. 20500

Dear Gil:

As you requested, I have reviewed the background of Section 361 of the Public Health Service Act (42 U.S.C. 264), its interpretation and application by the Food and Drug Administratior and the Public Health Service over the past several years, and its interpretation by the courts. Enclosed is a copy of each of the documents to which reference is made in this letter, to facilitate your own evaluation.

I

The original Federal communicable disease law was passed by Congress in 1893 (27 Stat. 449). As you will see, Section 3 authorized the Supervising Surgeon-General of the Marine Hospital Service, Department of the Treasury, to issue regulations to prevent the introduction of contagious and infectious diseases into one state from another. Unfortunately, I have not had the opportunity to research and review the legislative history of this Act, and therefore cannot provide information on the specific congressional

intent. It appears from the wording of the statute itself, however, that the Department of Treasury was given very broad and all-encompassing authority to prevent the spread of disease.

II

In 1944 Congress consolidated and revised all of the laws relating to the public health service in the Publish Health Service Act (58 Stat. 682). (A copy of relevant portions of the House Report on that bill, as reproduced in 1944 U.S. Code and Congressional Service 1211, is enclosed. Section 361, which was later codified in the United States Code as 42 U.S.C. 264, is discussed on pages 1214 and 1234-1235.)

As you know, Section 361, as enacted in 1944, provides broadly that:

> "(a) The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pestic stermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary."

In addition, Section 368(a) provides that "Any person who violates any regulation prescribed under sections 361 . . . shall be punished by a fine of not more than $1,000 or by imprisonment for not more than one year, or both."

The wording of Section 361 is uniquely broad. By its terms, this provision authorizes HEW to promulgate any regulations necessary to prevent communicable disease, and

to provide for inspection and any other enforcement measures that may be necessary. The legislative history does not detract from the broad statutory language. The House Report states that the "confusing limitations" in the 1893 Act were intentionally eliminated and that the new law was intended to "expressly sanction the use of conventional public-health enforcement methods" as well as to "authorize destruction of contaminated articles or infected animals which are dangerous to man, in those cases where no other disposition is safely possible."

Thus, there is no tenable argument that Section 361 was intended narrowly to be limited only to quarantine of human beings or humans and animals (since the law encompasses all "articles," a term commonly used in regulatory statutes to encompass all substances or objects of any kind), nor is there any argument that inspection is not permitted (since it is specifically mentioned) or that a wide range of other enforcement mechanisms is not authorized (since the law permits any "other measures" for carrying out and enforcing any regulations as in the judgment of HEW may be necessary).

III

Questions have been raised about the application of Section 361 to intrastate (as contrasted with interstate) commerce. Questions have also been raised as to whether Section 361 can be interpreted to authorize the prohibition (as contrasted with the regulation or control) of specified activity. Both of these issues have now been definitively resolved in a 1977 court decision upholding the legality of an FDA regulation banning all small pet turtles from both intrastate and interstate commerce under the sole authority of Section 361.

In the Federal Register of April 7, 1972 (37 F.R. 7005), FDA proposed a prohibition of the importation of small pet turtles, and a requirement of bacteriological testing and certification for interstate shipment of such turtles, in order to prevent the spread of salmonella. This regulation was made final in the Federal Register of November 18, 1972 (37 F.R. 24670).

On the basis of additional information showing that the certification program was not effective, FDA issued two

additional alternative proposals in the Federal Register of May 28, 1974 (39 F.R. 18463) that would either prohibit the sale and other distribution of small pet turtles or would improve the certification scheme and impose additional requirements on the sale and shipment of these turtles. In discussing the first of his two alternative proposals in the preamble, the Commissioner stated that:

> "Under the Public Health Service Act, the Commissioner has the authority to extend a prohibition on distribution to all turtles and turtle eggs, whether or not they have passed through interstate commerce, if in his judgment such a complete ban would be necessary for effective control over the interstate spread of turtle-associated diseases." 39 F.R. at 18464.

On the basis of the comments received, the Commissioner issued a final regulation in the Federal Register of May 23, 1975 (40 F.R. 22543), banning all such turtles from intrastate and interstate commerce. In paragraph 13 of the preamble, on page 22545, the Commissioner specifically rejected a suggestion that the turtles should be banned from interstate shipment but should be permitted for intrastate shipment.

Subsequently, the State of Louisiana brought suit to enjoin enforcement of this regulation on a variety of legal grounds. In State of Louisiana v. Matthews, 427 F. Supp. 174 (E.D. La. 1977), the Court upheld the legality of the regulation against all challenges. Specifically, the Court ruled that FDA could properly ban all small turtles rather than only those turtles shown to be infected and thus to be health hazards, on the ground that "Congress has granted broad, flexible powers to Federal health authorities who must use their judgment in attempting to protect the public against the spread of communicable disease." The Court rejected, as unproven, a contention that less drastic means of regulation would be sufficient to protect the public. It ruled that Section 361 permits FDA to control intrastate as well as interstate activity. Finally, it rejected a contention that the regulation is discriminatory because there are

no other comparable regulations. (For another court decision broadly upholding the discretion of HEW to enforce Section 361 see United States v. Shinnick, 219 F. Supp. 789 (E.D. N.Y. 1963).)

IV

Section 361 has been applied by the Public Health Service and FDA in the past in a wide variety of ways. In general, the Public Health Service was responsible for implementation of Section 361 until the late 1960s when responsibility for implementation of its foreign aspects were delegated to CDC and for implementation of its domestic aspects relating to the law enforcement functions of FDA were delegated to FDA. (Copies of the current regulations issued under Section 361 by the Public Health Service in 42 C.F.R. Parts 71 and 72, and by FDA in 21 C.F.R. Parts 1240 and 1250, are enclosed. Do not be misled by the citation, as legal authority for these regulations, of Section 215 of the Public Health Service Act; that provision merely authorizes HEW to issue regulations to implement the Public Health Service Act.)

As you will see, these regulations cover a wide variety of subjects. They deal in detail with the sanitation of interstate conveyances. The Drinking Water Standards in 42 C.F.R. 72.201-207 relate not just to bacteriological quality, but also to physical and chemical characteristics which surely would not fall within any narrow definition of the concept of a "communicable disease." The Drinking Water Standards have been enforced as the national standard since 1962.

Etiologic agents are defined, and their transportation regulated, under 42 C.F.R. 72.25. Psittacine birds, lather brushes, and plain garbage are regulated under 21 C.F.R. 1240.65, 1240.70, and 1240.75, as a prophylactic measure to prevent disease.

For many years, the Public Health Service, and more recently FDA, has engaged in joint programs with State and local government agencies and with the regulated industry to promote sanitation in the production of milk products and shellfish, and in the provision of food in eating establishments, under the general provisions of Section 361. Development of the Pasteurized Milk Ordinance and Code, through the

Interstate Milk Shippers Conference, has had a major impact on milk sanitation. The PMO provides detailed requirements for the handling of milk and dairy products on the farm, in order to prevent the possibility of communicable disease. The growing conditions for shellfish have similarly been the subject of control since 1924 under the National Shellfish Sanitation Program, and FDA has proposed to establish regulations codifying this program in the Federal Register of June 19, 1975 (40 F.R. 25916), which are now being held in abeyance pending further study required by Congress in Section 16(b) of PL. 94-370 (90 Stat. 1013, 1033). FDA proposed to codify its 40-year history of cooperation on food sanitation programs for food service establishments in the Federal Register of October 1, 1974 (39 F.R. 35438), and has since concluded instead to issue a model ordinance as announced in the Federal Register of March 22, 1977 (42 F.R. 15428). Under the same authority, FDA has announced a proposed Model Retail Food Store Sanitation Ordinance in the Federal Register of October 25, 1977 (42 F.R. 56367) and a Model Vending of Food and Beverages Ordinance in the Federal Register of October 7, 1977 (42 F.R. 54626).

Finally, in a variety of regulations in the past few years designed to implement a national blood policy, FDA has utilized Section 361 to control blood banking and blood labeling practices in intrastate as well as interstate commerce. The preambles to these regulations specifically mention the need for close control of all blood practices, in minute detail, in order to prevent communicable disease. Copies of the proposed regulations to establish current good manufacturing practice for blood and blood components published in the Federal Register of May 28, 1974 (39 F.R. 18614) and to require a label statement to distinguish volunteer from paid blood donors published in the Federal Register of November 14, 1975 (40 F.R. 53040), both of which discuss this subject, and both of which provide extraordinary detailed requirements, are enclosed.

V

Questions have been raised about the degree and nature of the potential harm that must be shown in order to invoke the authority of Section 361. It appears that the language of the statute itself, its legislative history, and the court

opinion interpreting it, place broad discretion in HEW to determine when the scientific evidence warrants reliance on Section 361 to prevent the possibility of communicable disease. Absent evidence that the HEW decision is wholly irrational, it is highly likely that the courts would uphold this exercise of discretion.

Nor is there any limitation in Section 361 on the source from which the potential harm must come in order to justify regulation. The terms of Section 361 permit regulation of research or of commercial activity. Indeed, the present regulations governing transportation of etiologic agents directly affects basic research, and a number of regulations affect commercial activity. The law permits control of human beings, animals, plant material, and any other form of article, in order to prevent communicable disease.

With specific reference to research on recombinant DNA molecules, the question has been raised whether there is sufficient danger of communicable disease to justify invocation of Section 361. If indeed there is no significant possibility of this occurring, it is difficult to understand why the United States Congress, NIH, the entire scientific community, numerous state legislatures and city councils, and many citizens groups, have been spending such an inordinate amount of time debating it. The very nature of the controversy itself is sufficient, in my judgment, to establish the potential for harm that is required under Section 361. If that potential were agreed not to exist, the entire issue of regulatory control over this research would never have been raised in the first place.

More specifically, some have questioned whether controls over certain types of research on recombinant DNA molecules, such as research on plant materials, can be justified under Section 361, since arguably the need for control arises from potential communication of disease from one plant to another rather than to man. Others have argued, however, that so little is known about research on recombinant DNA molecules that there is indeed a danger, which will remain until further experimentation proves otherwise, that research on plant materials could unleash pathogenic organisms to infect man, or could otherwise result in human infection in ways we cannot anticipate. Again, the mere

existence of this controversy, which has been sufficient to engage the attention of the entire country, seems quite enough to provide a legally sufficient basis for invoking Section 361. Moreover, once jurisdiction is established the courts have held that the National Environmental Policy Act provides substantive authority over all environmental aspects of the matter. Environmental Defense Fund, Inc. v. Matthews, 410 F. Supp. 336 (D.D.C. 1976).

It is important, once again, to understand that Section 361 was intended by Congress broadly to authorize prophylatic public health measures to prevent disease before it occurs. All that is needed to support regulations under this provision is either apprehension or uncertainty about the possibility of potential harm, the lack of adequate information showing that the harm cannot occur, and the possibility that the harm would be serious (e.g., irreversible) if it did occur. The more serious the nature of the potential harm, the less is required in the way of apprehension or uncertainty about that harm in order to justify invoking regulatory controls under Section 361.

VI

Questions have also arisen about enforcement of any regulations issued under Section 361. Section 361 itself provides that any articles not in compliance with such regulations may be destroyed, and authorizes any other enforcement measures that may be concluded to be necessary. In initially promulgating its turtle regulations, FDA included a requirement for bacteriological testing and certification. In its proposed shellfish regulations, other enforcement mechanisms were included. Each of the PHS and FDA regulations issued under Section 361 has its own tailor-made enforcement provisions.

Its seems clear that the statute authorizes regulations that require destruction of any materials resulting from activity not in compliance with regulations issued under Section 361. There is judicial authority for proposition that a Federal court, using its broad equitable powers, may enjoin violation of any validly-promulgated government regulation. Section 368 specifically provides for a fine and/or criminal incarceration. Section 361 specifically

mentions authority for inspection as an enforcement tool. Administrative provisions requiring reports or imposing other enforcement mechanisms are also clearly authorized. Thus, it appears that there is an infinite variety of enforcement mechanisms available, and that any of a number could be incorporated into a regulation promulgated under Section 361.

VII

Questions have been raised about the way in which the recombinant DNA research guidelines could be enforced if they were proposed and promulgated as regulations under Section 361. Clearly, it would not be necessary that the same government agency issue the regulations and enforce them. It would be possible, for example, for NIH to issue the regulations (as it presently does), and for CDC to enforce them. I mention CDC because it has jurisdiction over the Clinical Laboratories Improvement Act and thus has experience in inspection and enforcement with respect to scientific laboratories. FDA might also be in a position to enforce the regulations, but its other responsibilities are so overwhelming that enforcement of recombinant DNA research regulations might better be performed by CDC.

VIII

At the recent NIH meeting, representatives of the pharmaceutical industry stated that industry intends to comply with the NIH guidelines and would have no objection to making them mandatory if certain specific problems were overcome. The principal problem involved their concern about submission of trade secret information to NIH. I stated at that meeting that this issue exists with respect to all regulatory agencies, and that FDA, EPA, and the others have resolved it without significant difficulty.

A Federal statute, 18 U.S.C. 1905, explicitly provides that trade secret information provided to the government may not be released to the public by any government employee under pain of criminal penalty. FDA -- which regularly receives trade secret information from the regulated industry with respect to food additives, new drugs,

biological products, medical devices, and so forth -- has issued extensive regulations providing that such trade secret information will be held in confidence by the agency and will not be released to the public. Enclosed is a copy of 21 C.F.R. Part 20, dealing generally with the release of information from FDA to the public, together with Section 314.14 relating to information in IND and NDA submissions (as an example of the way in which this information is handled). The courts have now definitively held that 18 U.S.C. 1905 does in fact protect all trade secrets from public disclosure by government agencies. Thus, all that is needed to resolve this concern of industry is to incorporate some of the routine practices for protection of trade secrets, that have long prevailed in other governmental agencies, into the regulations governing recombinant DNA research.

Sincerely yours,

Peter Barton Hutt

PBH/mh

Enclosures

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
77 MASSACHUSETTS AVENUE
CAMBRIDGE, MASSACHUSETTS 02139

DEPARTMENT OF BIOLOGY
PHONE: (617) 253-1000
Room 56-721

March 14, 1978

Dr. Wallace P. Rowe
Laboratory of Viral Diseases
Bldg. 7, Rm. 304
National Institutes of Health
Bethesda, MD 20014

Dear Wally:

In the course of my dealings with the Office of Recombinant DNA Activities (ORDA) I have become concerned about the way in which that office interacts with the active workers in the field. In accord with the revision of the guidelines now in progress, I think that feedback from the active researchers in the field to the Recombinant DNA Committee might be in order, so that the "Roles and Responsibilities" section of the Guidelines might also be updated to maximize research efficiency and minimize senseless bureaucracy while still ensuring safe practice in the research. What I propose is a meeting of your Committee with Biohazard Officers and Principal Investigators at universities where recombinant DNA research is actively being pursued.

Our experience at M.I.T. suggests the following:

1. The principle of primary oversight by the local biohazard committee is being steadily eroded by pre-emption of decision power by ORDA. A typical instance is approval by the University Committee of a proposal followed by months of delay at N.I.H., leaving the researcher in limbo. The power of the local committee to approve research is clearly stated in the current Guidelines as written, but the ORDA seems to behave as formal approval is required from them even for obvious cases and for minor variances such as change of vector or protocol. I believe that the local committees should be encouraged to take responsibility; if they are robbed of all their authority, they will quickly become useless. The precedent of Human Experimentation seems a good one - N.I.H. should have ultimate say, but the local approval should suffice in the absence of ambiguities.

2. Off-the-cuff opinions given by people in ORDA are inadvertantly inhibiting research. A good example of this is the yeast host situation: instead of going ahead and approving the decision of the local committee or seeking a determination from the Committee, applications were held up. Only a clever bureaucratic strategem

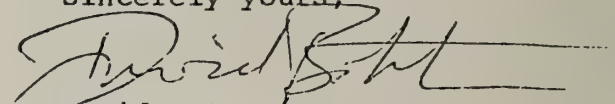
at NSF allowed a breakthrough in this particular logjam. It seems to me that the limits of ORDA's policy-making authority should be clearly defined in light of its limited scientific expertise, and questions of interpretation of the guidelines should be referred to the Committee rather than commented upon. Possibly such interpretative authority should be granted, in a limited way, to the local committees, as is the case in Human Experimentation. Whatever happened to the role of the Study Sections in this process?

3. The Memoranda of Understanding should be simplified. As it is now, the pronouncements in the N.I.H. Guide make it appear that each experiment requires a new MUA, even if the investigator already has an approved P2 or P3 facility. It should be possible to allow an approved facility to operate within the entire range of permissible experiments at the approved level of containment. After all, if one has an MUA for any P3 experiment, then it seems a good assumption that the Principal Investigator and his local committee are well-informed. Why not allow the local committee to have latitude within the entire range of permissible experiments, relying upon it to submit marginal cases to ORDA, rather than making everyone go through all the paperwork every time anew? Perhaps a published list of permissible shotgun experiments should be published along with the appropriate containment and updated as new MUA's are approved by ORDA. Then the local committees could have explicit guidance in this area and could act without ambiguity on all proposed experiments involving these DNAs.

This is only a sample of my own thinking. In order to get a realistic idea of how the Guidelines are working in practice, and to inform the Recombinant DNA Committee of the problems and opportunities for simplification, I urge you to consider a meeting along the lines I suggested above.

Thanks for your patience, and please let me know if there is anything further I can do in this matter.

Sincerely yours,



David Botstein
Associate Professor of Genetics

DB:po

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOCHEMISTRY
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Area Code 415
497-6161

March 27, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This letter is in reference to recent decisions by the NIH concerning the administration of recombinant DNA research.

I strongly feel that the bureaucracy surrounding the NIH Guidelines for recombinant DNA research has now become so unwieldy that many important research programs have been seriously curtailed. The recent decision that all MUAs must be approved by a central office completely undermines the original concept of local panels for control. I am sympathetic to the problems of the Office of Recombinant DNA. I also understand the desire for a consistent and uniform procedure for all research. However, I think it is time that all parties involved - Office of Recombinant DNA, local recombinant DNA panels and research scientists - openly discuss methods by which the concerns of all could be best met. The bureaucracy surrounding the Guidelines must be designed for simplicity and effectiveness, and I think this can be done. I am willing to present some ideas if there is a reasonable chance that they will be considered.

Sincerely yours,

Ronald W. Davis

RWD/lh

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
77 MASSACHUSETTS AVENUE
CAMBRIDGE, MASSACHUSETTS 02139

DEPARTMENT OF BIOLOGY
Room 56-721
PHONE: (617) 253-1000

April 3, 1978

Dr. Donald S. Fredrickson
Director
Bldg. 1, Room 124
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

As you suggested in our conversation last week, I am writing to summarize the arguments in favor of giving some well-defined status in the revised NIH Guidelines for Recombinant DNA Research to in vitro recombination experiments involving bacteria known to exchange chromosomal DNA in nature. As you know, the present draft revision regards these experiments as outside the purview of the guidelines, presumably because they do not result in novel combinations of genetic information and thus present no special hazard. I agree absolutely with the judgement of no special hazard, but I am afraid that excluding these experiments from the guidelines NIH will leave them in a bureaucratic limbo which potentially can cause difficulty for both the experimenter and NIH.

I propose instead that the Guidelines include these experiments (including "self-cloning") explicitly, but in a category of experiment ("HV-O", and/or "P-O"?) requiring no precautions beyond the prudent bacteriological practice appropriate to the handling of the microbial species involved. Thus a Salmonella cross with E. coli would be considered no more hazardous than Salmonella, and no additional precautions need be demanded by NIH. Bureaucratically, I can envision several possibilities. A purely pro forma MUA might be required, or else a simple notice of the experiments to NIH with an acknowledgment. Alternatively, all paperwork could be forgone entirely. The important point, in my view, is that the experiments be explicitly recognized as recombinant DNA (which they logically are) and explicitly be recognized as presenting no special hazard.

The advantages of this explicit approach over exclusion of these experiments are the following:

1. NIH will retain continuing control over them in principle, making more rational its intention to identify "exchangers" versus "non-exchangers" and, more important, lending its protection to these experiments. The latter will be of special importance in the event that legislation carrying a useful pre-emption clause is passed.
2. NIH will immunize itself (and the investigators) from the charge that a potentially dangerous class of experiments has been left unregulated and unmonitored. After all, it should be anticipated that some highly pathogenic species of bacteria can be shown to be "exchangers" with E. coli.

If NIH retains its surveillance of these, it can remove them from the HV-O category for cause, on a case-by-case basis, without the nasty problem of defining some experiments as recombinant DNA and others not simply on the basis of bacterial species.

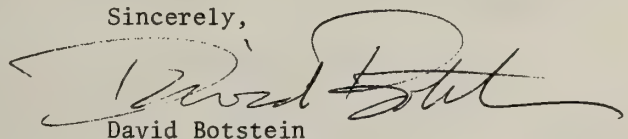
3. Flexibility is retained in this area, since the criterion of "exchanger" may in fact change as more is learned about natural mechanisms of genetic exchange in nature. I can imagine in the future one might want to place some experiments now in the HV-1, P-1 class into the HV-O, P-O class on the basis of a finding of natural exchange. In the absence of any such explicit category, one would have to say that such experiments suddenly stopped being recombinant DNA, which to me seems illogical and which might be hard to defend publicly.

4. NIH can avoid the potentially burdensome problem of having to define, in an absolute way, difference between "pathogens" and "non-pathogens". This is, as we all realize, a relative matter. By retaining explicit surveillance, NIH can grade the level of containment for exchangers according to some realistic determination of the degree of pathogenicity, without having to rule in or out absolutely a marginal case. Under the existing draft revised Guidelines there is no good way to deal with a weakly pathogenic species which is an exchanger or a non-pathogenic strain of a bona fide pathogen. Retention of these experiments under the guidelines should allow satisfactory arbitration of these kinds of problems.

In closing, I would like to urge that whatever is decided, the large class of experiments unfortunately and unintentionally forbidden by current guidelines (e.g. Salmonella and Klebsiella self-cloning) be explicitly permitted (if only by mention as examples) in the language of the new revised quidelines. Only in this way can I see justice for those of us who, by indirection and political expediency, have been denied the fruits of recombinant DNA technology for the past several years.

Thank you again for your consideration. It was kind of you to see me and to listen to our problems.

Sincerely,



David Botstein
Associate Professor of Genetics

XC: Dr. S. Gottesman
Dr. W. Rowe
Dr. W. Gartland

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

School of Medicine
Department of Microbiology and Immunology, SC-42

April 4, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I would like to propose for consideration of the Recombinant Advisory Committee the following addition to the list of prohibited experiments (section IIIA.ii of the revised Guidelines):

> "Formation of recombinant DNAs containing genes for the biosynthesis of potent toxins (e.g. botulinum or diphtheria toxins, psilocybin, venoms from insects, snakes, etc.)."

The justification for inclusion of psilocybin in the list of potent toxins that would be hazardous products of cloned DNA is as follows: Psilocybin is a simple fungal metabolite whose effects on animals are potent. It is formed from tryptamine, a normal metabolite of higher organisms, by one or two simple enzymatic steps (S. Agurell and J. L. G. Nilsson (1968), Biosynthesis of Psilocybin II: Incorporation of Labeled Tryptamine Derivatives. Acta Chem. Scand. 22, 1210.). Thus the cloning of DNA from Psilocybe spp. or Panaeolus spp. in E. coli could create a strain that synthesizes this drug. Escape of such a recombinant DNA could be disastrous.

If this cloning experiment is not included in the list of prohibited experiments, I would suggest that it be specifically mentioned under section IIIB.e.1 as a P3EK2 experiment, and the language be changed to include toxins other than polypeptide toxins.

It is advisable to include specific mention of this issue in the guidelines because the potential hazard is not immediately obvious, and the substance psilocybin, while not a "potent polypeptide toxin," nevertheless poses just as serious a problem because of its simple mode of biosynthesis.

Thank you for considering this point.

Sincerely yours,

Mary-Dell Chilton

Mary-Dell Chilton
Research Associate Professor

G305 Health Sciences Building / Telephone: (206) 543-5824

Dr. Donald S. Fredrickson, Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Enclosed is a copy of the report of the Workshop on Risk Assessment of Agricultural Pathogens held in Washington on March 20-21, 1978. This meeting, which was cosponsored by the NIH, NSF and USDA, was attended by 12 invited participants and about 20 others, who served as liaison representatives from various government agencies or as observers. The invited participants had collective expertise in all of the major disciplines in plant pathology, and one has worked with baculoviruses. Only 5 have a direct involvement in recombinant DNA research. A list of participants and government liaison representatives is appended to this letter.

The primary purpose of the meeting was to assess the risks accompanying the use of recombinant DNA technology with agricultural pathogens. Our discussions covered plant pathogens and baculoviruses. We considered that risk assessment here entails a consideration of different concerns than those applied to risk assessment of research with man and animals and we were of the collective opinion that with a few specifically enumerated precautions, the risk to man and to animals is minimal. Consequently, we have recommended a lowering of containment levels in a number of instances.

Our discussions dealing with certain types of experiments were clouded by our uncertainty as to what will be the accepted definition of genetic exchangers which will eventually result in elimination of some organisms from the guidelines. We have anticipated two alternative situations and have presented our recommendations for both.

We are forwarding a copy of this report to Dr. Gartland's office for consideration at the April 27-28 meeting of your Recombinant Advisory Committee.

Yours sincerely,

Peter Day & M.Z.

Peter R. Day
Department of Genetics
Connecticut Agricultural
Experiment Station

Milton Zaitlin
Department of Plant Pathology
Cornell University

[See Appendix G to "National Institutes of Health Environmental Impact Assessment," Federal Register, p. 33174, July 28, 1978.]

Attachment

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COLLEGE OF NATURAL RESOURCES
AGRICULTURAL EXPERIMENT STATION
DEPARTMENT OF PLANT PATHOLOGY

April 13, 1978

Dr. Donald Frederikson, Director
National Institute of Health
Department of Health, Education &
Welfare
Bethesda, MD 20014

Dear Dr. Frederikson:

On March 20th and 21st, 1978, I participated in the NIH-NSF-USDA workshop to discuss risk assessment of agricultural pathogens. Whereas I support the recommendations made in our report I want to submit a minority opinion concerning a recommendation (middle of page 9) of that report, referring to section II.D Biological Containment - Host Vector Systems. a.2. Other Procaryotes (P49600) of the Federal Register. Sept. 27, 1977 part III Draft. Our Committee endorsed the La Jolla Working Group Draft. In the event that sections iii and iv are not adopted we proposed that:

(i) The use of an indigenous plasmid or bacteriophage (vector) shall be exempt from the Guidelines.

(ii) The use of a foreign vector (a non-indigenous plasmid or bacteriophage) from an organism which exchanges DNA by natural physiological processes shall require P2 containment.

This distinction is basically similar to the La Jolla Working Group recomendation iii. It is not supported by the rationale which was proposed (namely, that:"Many self-cloning experiments with agriculturally significant bacteria could be more readily and safely carried out by using well characterized E. coli plasmid vectors").

I do not support this distinction between indigenous and non-indigenous vectors for self-cloning purposes because I consider it to be largely arbitrary, wasteful and almost meaningless. It suggests, for example,that ColEl derivatives are less safe as vectors in Enterobacteria other than E. coli or in other hosts in which they may yet be shown to replicate. An indigenous vestor is almost certainly less well adapted to a laboratory host than to its natural host - therefore less likely to perpetuate the recombinant molecules stably in the former case than in the latter. In either case the "self-cloned" recombinant molecules can be expected to integrate into the chro-

mosome of the host used since they will share homologous sequences. Furthermore, It will be a waste of time and money,and will defeat the purpose of the Guidelines, if researchers were forced by such a distinction to develop a new "natural" vector for every new bacterium simply to avoid regulations.

Respectfully,

N.J Panopoulos

Nickolas J. Panopoulos, Ph.D.

Assistant Plant Pathologist, Lecturer

Copies forwarded to:

W. H. Gartland
P. R. Day
M. Zaitlin
A. Kelman
C. I. Kado
A. K. Vidaver
F. Ausubel
M. Chilton
D. Coplin
R. Millar

UNIVERSITY OF CALIFORNIA
SAN FRANCISCO
ACADEMIC SENATE

April 14, 1978

Dr. Donald S. Frederickson
Room 124, National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Frederickson:

RE: Recombinant DNA approval procedures as described in NIH Guide for Contracts & Grants, February 15, 1978

The NIH Guidelines for Recombinant DNA are a unique example of self-regulation within the scientific community. Investigators have, of their own volition, called attention to potential hazards in biological research and instituted a procedure of self control to regulate the limits within which safe experimentation can proceed. We, as members of the UCSF Biosafety Committee, wish to express concern that there are now two divergent systems to which attention must be paid. On the one hand the NIH Guidelines dictate the general areas of classification of physical and biological containment and prescribe the use of the certified vectors and host cells by which research may be locally regulated. On the other hand the procedural mechanism by which these guidelines are administered, as described in the NIH Guide for Grants and Contracts, Volume 7, Number 3, February 15, 1978, establish a restricted centralized system of regulation.

Our concern is that although the original intention of the NIH guidelines was to depend upon the self-regulatory concept underlying the peer review system of scientific investigation, in practice the Guide for Grants and Contracts sets out a procedure which removes self-regulatory authority from local committees and centralizes power for recombinant DNA experiments in the hands of a small number of people in the Office for Recombinant DNA Activity (ORDA) in Washington. No experiments in recombinant DNA can be carried out on federally-funded grants without the prior approval of the individual experiments by ORDA, NIH. The centralization of such power undermines both individual investigator's responsibility and Biosafety Committee responsibility. In effect, the local committee is now required to act as a dummy committee since local approval of any recombinant DNA experiment has no authority. The local committee can only funnel a request to ORDA and await their disposition. The frustration of this situation has already led to one resignation from our committee with threats of more resignations.

There are already examples of self-regulatory committees that have local authority to deal effectively with more serious and obvious human hazards than recombinant DNA, e.g., radioisotope committees and human research committees. These are accorded considerable authority and their determinations are challenged at the national level only in the most obviously problematic cases. In the case of research involving human subjects the Office for

Protection from Research Risks (OPRR) exercises surveillance over local committees but does not itself approve individual protocols. This process of strong reliance upon local review has been endorsed by the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research.

We would like to recommend that the procedural mechanism for monitoring and approving recombinant DNA experiments should be delegated to individual institutional Biosafety committees, just as the authority for human research and radioisotope use is delegated. This would allow administration of federally-funded projects by the same method as non-federally-funded projects, i.e., ensure that physical and biological containment levels proposed by investigators are accurate and that the vectors and host cells to be used are certified. At that point local approval should be sufficient for experiments to proceed forthwith.

At present the requirement to send MUAs to Washington for every experiment involving recombinant DNA involves two to six months delay from the conception of the experiment to receiving approval to execute it. With the requirement for annual update of an MUA this means that some investigators will lose a quarter to a half of each year waiting for a response from ORDA. The suggestion to delegate real authority on individual MUAs to local committee would make the Washington Office of Recombinant DNA Activities into one involved with setting national policy, certification of approved vectors and host cells, and other national issues pertinent to recombinant DNA. It could also monitor the record of local committees to ascertain compliance with the appropriate regulations and guidelines.

Specific points at which we wish to raise criticism of the procedures set out in the NIH Guide for Grants and Contracts are as follows:

Page 8, part 4 - approval of MUAs: It is stated that the local committee only produces a proposed MUA and that recombinant DNA research is not funded until MUAs are approved by NIH. This centralizes the system and runs contrary to the concept of peer review and of delegation of authority for self-regulation. It puts undue power into the centralized system by which individual experiments are approved by a small number of people in Washington. We see no reason why individual institutional Biosafety committees should not have the power to approve MUAs consistent with the guidelines set by NIH. The need for centralized approval runs contrary to both the spirit of scientific research and to policies of NIH.

Page 9, footnotes 1, 2, and 3: If local Committees are expected to control the expenditure of funds as prescribed by these footnotes to grant awards according to approved MUAs an expensive monitoring system would be required to correlate expenditures on each biological and chemical item to approved MUAs. Also, these footnotes imply that it should be possible to identify those reagents which are used for recombinant DNA and those which are not. The implications of these footnotes are quite unrealistic, especially when investigators have multiple grants and the definition of each type of expenditure and its correlation with MUAs requires a purchasing system wchich this and other institutions do not possess.

Page 9, part 5: In this section the necessity to obtain approval at NIH level for changes in currently funded projects is excessively restrictive since even the most limited change in DNA, i.e., even one base pair change in a DNA segment (as specified in number 5) requires approval at NIH level. This restricts individual investigators and interrupts the traditional flexibility of the grant system which allows changes and modifications to experiments in progress according to the acquisition of new information. The requirement to wait and refer every change to NIH and to wait for an approved MUA to return imposes exceptional delay.

We offer these suggestions, particularly the plea for genuine jurisdiction by local committee, in hope that a more effective system of review can be initiated. It is our fear that lessening of authority and discretion of local committees will lead to frustration by investigators and reviewers alike. In addition, an effective review process should be consistent with, rather than contradictory to, the intrinsic nature of scientific work.

Sincerely,

James E Cleaver

James E. Cleaver, Ph.D.
Chairman
Biosafety Committee

EH

CC; Dr. W. Gartland
Dr. D. Kamely
Vice Chancellor Chater
Chancellor Sooy

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COLLEGE OF NATURAL RESOURCES
AGRICULTURAL EXPERIMENT STATION
DEPARTMENT OF PLANT PATHOLOGY

BERKELEY, CALIFORNIA 94720

April 14, 1978

Dr. Donald Frederikson, Director
National Institutes of Health
Bethesda, MD

Dear Dr. Frederikson:

In an earlier letter (dated Dec. 9, 1977) I had written to you concerning the proposed revisions of the NIH Guidelines. Since then I have given additional thought to the points which I raised and feel rather strongly that they should be brought to the attention of the RAC Committee, something which my first letter apparently did not accomplish. Accordingly, I am submitting a new summary letter to you and to individual members of the Committee for consideration at the next available opportunity.

General comments:

It is clear that the basic revisions proposed are meaningful and overdue. The original stringency has already caused much unnecessary delay in certain areas of research. This I have had the ill fortune to experience personally. However, if the Guidelines are to be respected and followed by scientists they should take into account, in my view, (i) the comparative biosafety of in vivo and in vitro methods of accomplishing particular experimental goals (e.g., the construction of a particular strain particularly in gram-negative procaryotes), and (ii) the possible indirect consequences of over-regulating the in vitro over the in vivo method. The latter, of course, being "natural" and not having caused any serious biosafety problems to my knowledge after 25 years of use, should not be regulated.

Specific comments:

(1) La Jolla Working Group Draft--Recommendation III. This recommendation proposes to deregulate self-cloning (which I fully support) whenever the vector is indigenous to (found in nature in) the host used. It is implicit that self-cloning using non-indigenous vectors will not be deregulated. This distinction I do not support because I consider it largely arbitrary, wasteful and almost meaningless. It suggests, for example, that all ColE1 derivatives are less safe as vectors in Enterobacteria other than E. coli or in other hosts in which they may yet be shown to replicate. An indigenous vector must certainly be less well-adapted to the laboratory host than to its natural one--therefore less likely to perpetrate the recombinant molecules stably in the former case than in the latter.

Many self-cloning experiments with agriculturally significant and other gram-negative bacteria could be more readily and safely carried out by using well-characterized E. coli plasmid vectors. Some organisms may not have usable vectors. It will be a waste of time and money if researchers choose to develop a new "natural" vector for every new bacterium only to avoid regulations.

(2) La Jolla Group Recommendation IV. The list of "exchangers" among gram-negative bacteria should not be restricted to "chromosomal exchangers" but should include organisms that exchange any DNA (exceptions for CDC classes 3 and 4).

This can be justified easily on the grounds that in vivo methods are applicable to most, if not all, members of this group. Furthermore, in vitro genetic manipulations in these bacteria do not pose substantially greater biohazard than in vivo genetic manipulations. In many cases, the in vitro methods can be judged as safer than the in vivo.

For example, many researchers use the P-plasmids as conjugative vehicles in a variety of bacteria. These plasmids transfer to almost any gram negative species and recombine with bacterial chromosomes and other plasmid replicons. P-prime derivatives of these plasmids carrying segments of chromosomal material from diverse organisms have been obtained in vivo. Recently, P-plasmid -Mu phage cointegrates have been used to induce the transposition of bacterial chromosomal segments into P-plasmids. Secondary transmission of these conjugative P-prime elements cannot reasonably be judged as less probable than of in vitro recombinant plasmids the vectors of which are non-conjugative and have a much more restricted host range than the P-plasmids. Furthermore, conjugation allows for the transfer of extended regions of "donor" DNA, whereas individual in vitro recombinant plasmids are likely to carry only short segments of "donor" DNA. Formation of plasmid-primes in vivo is generally mediated by IS sequences. These subsequently promote recombination and integration. DNA fragments cloned in vitro will not generally contain neighboring IS sequences from the donor chromosomes. With this perspective I find it hard to justify the fact that NIH should, for example, regulate the cloning of Rhizobium DNA in E. coli when isolation and handling of RP4-primesis rightly left up to the individual investigator.

If political expediency at this moment or other arguments dictate the approval of a restrictive "chromosome exchanger" list rather than the liberal "plasmid exchanger" one, plasmid-prime mediated transmission among gram negative bacteria should be regarded as equivalent to other forms of chromosomal gene transmission.

(3) Definition of HV-1 Systems. The revised guidelines (Fed. Reg. Sept. 21, 1977, Part III, p. 49600, column 2, paragraph 2 "other procaryotes"). explicitly prohibit conjugative plasmids and generalized transducing phages in EK-1 and HV-1 systems. It is implicit that these elements shall not be introduced subsequent to cloning. Literally interpreted, this precludes, for example, vector host range tests in nontransformable species of bacteria. It also prevents plasmid-promoted mobilization to introduce recombinant molecules from a primary cloning host back to the original DNA source organism or its mutants. This will effectively preclude complementation tests for traits not expressed in the cloning host, such as plant-bacterium interactions in symboisis or pathogenicity. Even in transformable species,

mobilization is generally simpler and easier to perform than transformation which requires prior isolation of the DNA molecules. Mobilization tests are also essential during vector construction experiments. In effect, this provision creates a dilemma. In the proposed revisions, in which self-cloning using indigenous plasmids will be excluded from regulation, the recombinant DNA can be mobilized out of the host strain into other procaryotes. On the other hand, DNA cloned from the same donor procaryotes into a different recipient procaryote cannot be mobilized by a conjugative plasmid back into the original donor, despite the fact that the latter will be receiving its own DNA by this procedure.

If the "exchanger" list is based on plasmid exchange these arguments are irrelevant. However, if the list is based on chromosomal DNA exchange the present wording in the definition of HV-1 systems will turn out to be very restrictive and unreasonable in view of the proposed deregulation of self-cloning. Since the P + HV containment levels assigned under the Guidelines are presumably commensurate with the probability that the cloning host may be converted into a pathogen, it is the secondary biohazards (runaway plasmids) that must be compared. Differences in the escape potential of recombinant plasmids from various unmodified (HV-1) gram-negative procaryotic primary cloning hosts, although habitat-dependent, can only be judged in very hypothetical general terms.

If a narrow definition of exchangers is adopted I suggest that allowance be made for conjugative mobilization in HV-1 systems when the DNAs are of procaryotic origin, either by changing the HV-1 definition or in some other appropriate fashion. For example, the level of physical containment could be increased one step. Alternatively, conditional suppressor-dependent conjugative plasmids could be used when the ultimate recipient does not contain a suppressor gene. Finally, a conjugative plasmid unable to replicate or establish itself in the ultimate recipient could be employed.

I hope that you and the Committee members give these matters adequate consideration.

Sincerely yours,

N.J. Panopoulos

Nick Panopoulos
Assistant Plant Pathologist, Lecturer

Copies forwarded to:

E.D. Adelberg
A. Campell
P.R. Day
S. Falkow
W.H. Gartland
S.K. Gottesman
D.R. Helinski
R.B. Hornek
L. Jacobs
E. Klutter
J.W. Littlefield
J.K. Settlow
J. Spizizen
E.S. Redford
W.P. Roe
D. Stetten
L. Walters
M. Zaitlin
D. Coplin

UNIVERSITY OF WISCONSIN-MADISON

COLLEGE OF AGRICULTURAL
AND LIFE SCIENCES

Department of Biochemistry
420 Henry Mall
Madison, Wisconsin 53706 USA
Telephone: 608/262-3026/262-3040

April 19, 1978

Dr. Donald Frederickson, Director
National Institute of Health
Building 1, Room 124
Bethesda, MD 20014

Dear Dr. Frederickson:

I have just returned from an international scientific meeting on plasmids in West Berlin. A number of U.S. scientists were invited to present their work at the meeting, which was funded by the European Molecular Biology Organization and the German Government.

The technology and applications of recombinant DNA research formed a significant part of the conference, and it became apparent that our European colleagues have made substantial advances usirg this technology. Although the basic scientific discoveries leading to the successful application of recombinant DNA methods to biology were made in U.S. laboratories, European scientists are applying these methods without serious restrictions to a wide variety of problems.

Thus, we learned of advances in the use of the recombinant DNA in studies of the synthesis of antibiotics and in studies of the metabolism of plant cells, for example, that could well lead to important developments in the production of new antibiotics and in the production of new and better foodstuffs. I say "without serious restrictions" because most European countries have much less stringent laws regulating recombinant DNA research.

In my own case, for example, we have made a number of discoveries that might be applied to the improvement of new and existing antibiotics. I would like to use recombinant technology to extend these studies, but I cannot. I do not have the facilities to do the necessary experiments according to the existing NIH regulations, and it would take a long time and much money (not available on my current grants) to obtain these facilties. The simplest solution, of course, would be to go and do the experiments in Europe.

Thus, I am writing to ask you to consider, very seriously, the effects that strict legislation of recombinant DNA research will have on many aspects of biological science in this country. We are already falling behind our European colleagues in many respects. German, Belgian, and British industry are setting up laboratories to pursue the application of recombinant DNA techniques to industrial problems. In my experience, I know of no U.S. pharmaceutical company that is committing the same kind of effort. It was pointed out at the conference that the Russian Government is to make a substantial investment into recombinant DNA research. Incidentally, several of the Russian scientists involved in this development received their training in U.S. laboratories.

I don't normally mind my European colleagues making important advances, but I do object when they make such advances because they can do experiments that I am banned from doing! I feel that we are being penalized by the existing regulations. I believe that the majority of experiments involving recombinant DNA are safe and that we are in a position to make significant advances in a number of areas that will be of considerable benefit to the welfare of man.

At the present time, we are on the threshold of operating under a Communistic system in our basic research where the Government determines what experiments can be done. The irony is that those countries, generally considered less free in other respects, are now taking advantage of our new discoveries, funded by NIH and NSF grants; while we have to sit back and watch, or try to devise schemes to get around the present guidelines.

Although the introduction of laws protecting constituents against the imaginary and science fictional hazards of recombinant DNA research may appear to be necessary, I question whether legislators like yourself have considered fully the implications of these laws on the execution and progress of basic and applied biological research in the U.S., with subsequent loss of benefit to the entire population.

I urge you to consider and reconsider proposed action on recombinant DNA research in the U.S. Senate and House. We must beware of the introduction of restrictive rules that we will be unable to reverse. The present guidelines are severe and are an impediment to the advancement of U.S. science. Relaxation, and not stringency should be your major action.

Thanking you in advance for your help,

Yours sincerely,

Julian Davies
Professor of Biochemistry

clw

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

School of Medicine
Department of Microbiology and Immunology, SC-42

April 19, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing you following my return from Europe after attending the International Symposium on Genetic Engineering held in Milan March 29-31, 1978 and the Plasmid Workshop held in Berlin from April 1-5, 1978. During the course of the meetings I consulted with a number of scientists about your request to prepare a documented list of microorganisms which are known to readily exchange genetic material under laboratory conditions or in Nature. I am glad to tell you that this material is being collated for transmission to the Recombinant DNA Advisory Committee.

On March 30, 1978 Professor E. S. Anderson, Professor M. H. Richmond and I held a meeting (our second) on Rick Assessment under the auspices of the Committee on Genetic Experimentation (COGENE) which was formed by the International Council of Scientific Unions. It was our unanimous concensus that we now have available sufficient data in man and livestock to show that:

a) the survival of E. coli K-12 sublines in man and animals is exceedingly low;

b) the frequency of transfer of self-transmissible plasmids from K-12 to resident gram negative flora of man occurs very rarely indeed;

c) that the frequency of transfer of plasmids from the resident flora to fed E. coli K-12 strains is extraordinarily low and;

d) that the frequency of mobilization of non-conjugative plasmids (the type actually used in DNA recombinant experiments) from K-12 to other enteric flora is not detectable under normal circumstances.

The combined monitoring data of several laboratories over a three year period has failed to demonstrate the colonization (indeed not even the detection) of K-12 strains in research workers and their families. Moreover, monitoring of the laboratory environment has not detected significant numbers of K-12 cells and in reconstructed accidental spills, the viable count of K-12 cells were found to decrease by 10 million fold in 4 hours if simply left to dry or was instantly sterilized if exposed to the mildest germicidal agents.

G305 Health Sciences Building / Telephone: (206) 543-5824

2. April 19, 1978
Stanley Falkow

I wish to emphasize to you that all of the monitoring, survival studies, and transfer experiments were performed with ordinary E. coli K-12 rather than the certified EK-2 strain, X1776. Hence, since studies with ordinary E. coli K-12 are found to be negative, X1776 must represent a rather good case of "overkill". Analogous EK-2 strains have been developed in Great Britain by Sidney Brenner.

Upon my arrival in Bristol, England in June, 1978 to begin my sabbatical leave from the University of Washington, I shall correllate the data from participating laboratories into a single paper that will be submitted for publication by September, 1978. I am glad to be able to tell you that the risk assessment monitoring has proved to be so uniformly negative. We would be pleased, of course, to learn whether you or others feel that further monitoring data is required. Of course, further risk assessment experimentation is required but hopefully this will address other questions of safety.

Aside from these positive aspects of my travel, I confess that, in another vein I found the meetings most distressing. It is painfully obvious that because of the very restrictive nature of the NIH guidelines, as well as the beauracratic wall that the guidelines have spawned, American biologists can no longer expect to keep pace with either Western European or East European science. That is not to say that other countries have not adopted research guidelines. They most certainly have. Yet, the guidelines adopted by the European community and the USSR retain a flexibility and a scientific reality that is absent from our own. Nor do I believe that the European or Soviets are any less concerned about safety than we. It seems, however, that they learned valuable lessons from our mistakes. It is difficult for me to convey to you the intense discomfort many of us felt when we heard the results of reasonable, totally safe experiments being described by Western and East European scientists that are now literally forbidden to U.S. scientists.

Perhaps the adoption of the pending revised NIH guidelines will rectify, in part, these discrepencies. It is unfortunate that the Congress has received a good deal of inaccurate information about the history of the guidelines and were subjected mostly to the two extreme views of recombinant DNA technology.

Many of us will continue to work towards a rational solution of the recombinant DNA controversy. Yet, there is but so much time that one can afford to spend on such "political" matters without giving up science and our obligations to our students and families. I believe I told you that most of us who were involved in the Asilomar Meeting and in drafting the first set of NIH guidelines could be described as "walking wounded". I thought many of my wounds had healed but, after this trip, I fear my wounds have been re-opened. I believe that if Congress passes legislation regulating recombinant DNA research, American biological science will be adversely affected for several years to come.

Although we are falling behind, it is a tribute to our younger scientists that they persevere in the face of beauracratic adversity and continue to perform brilliant, innovative experiments. But these young scientists are

beginning to lose their spark of excitement and they do not flourish. It is a pity.

I am glad on the one hand to send you news of our positive progress in one area; I regret that my news is not so encouraging in another (equally important) quarter. I am taking the liberty of sending copies of this letter to my congressional representatives and to several legislators considering recombinant DNA legislation. I doubt if it will have any impact but I shall sleep the better for it.

Sincerely,

Stan Falkow

Stanley Falkow, Ph.D.
Professor of Microbiology
and Medicine

csj

cc: Senator Henry Jackson
Senator Warren Magnuson
Senator Edward Kennedy
Congressman Joel Pritchard
Congressman Paul Rogers
Congressman Harley Staggers
Mr. John Stewart, Science Technology
and Space

OARDC
Ohio Agricultural Research and Development Center
WOOSTER, OHIO 44691
TELEPHONE (216) 264-1021

DEPARTMENT OF
PLANT PATHOLOGY

April 20, 1978

Dr. Donald Frederikson, Director
National Institures of Health
Bethesda,
Maryland 20014

Dear Dr. Frederickson:

I understand that the Recombinant DNA Advisory Committee will be meeting in the near future to consider the recommendations of the NIH-NSF-USDA workshop on risk assessment of plant pathogens. As a phytobacteriologist who is actively working in the area of bacterial genetics, I would like to add my opinion to those already expressed. I fully support the classification of plant pathogens set forth by the workshop participants and believe that recombinant DNA experiments with plant pathogenic bacteria (except those which are also known animal pathogens) do not present a greater risk to plant and animal health than experiments with any other group of bacteria. I am concerned, however, that the La Jolla Working Group's recommendations for exempted experiments, which the workshop endorsed, may present problems if the forthcoming list of "gene exchangers" (Recommendation IV) is not sufficiently broad. The problems arising from a narrow definition of gene exchangers have been outlined in Dr. N. J. Panopoulos' letter of April 14, 1978 to you and the advisory committee. I agree with Dr. Panopoulos' views and would like to emphasize some of the points that he has made.

In the past, research on plant pathogens has been directed mainly toward controlling diseases using empirical approaches rather than understanding the basic biology of the pathogens themselves. As a result these organisms are not well characterized from a genetic or biochemical standpoint. Developing a genetic system for these organisms by classical techniques has been a luxury that few plant pathologists could afford. This is especially true today in view of conservative agricultural research priorities and increased emphasis on fiscal

accountability. Fortunately, plasmid biology and recombinant DNA technology offer a short cut to doing genetics with uncharacterized species. These techniques allow one to investigate those characteristics unique to a species without wasting time repeating experiments that have already been done with E. coli. If recombinant DNA research with plant pathogens is not deregulated as fully as possible, then workers in this field will be required to either generate background data and documentation in order to get approval of an MUA or demonstrate gene exchange to prove that their organisms are exempt from regulation. In either case, there will be delays and the advantage of using recombinant DNA technqiues will be decreased. I fear that many qualified researchers in the agricultural sciences may not be able to afford or justify this time and effort and consequently some scientifically interesting and economically important systems will remain unstudied, certain aspects of my own research on Stewart's wilt of corn being a case in point. For this reason, I recommend that the committee define gene exchangers (La Jolla Group Recommendation IV) as those species which exchange any plasmids (or at least prime plasmids) so that the majority of plant pathogens will be exempt from the guidelines.

If, however, a narrow definition of gene exchangers is necessary for theoretical or safety reasons, then reconsideration of two other proposed restrictions would be advisable:

1) According to La Jolla Working Group Recommendation III self-cloning will be exempt only if carried out with indigenous vectors. I feel that the use of specific EK1 and EK2 certified vectors should be exempted in those species that exchange plasmids with E. coli. Developing new vectors for each species will be a time consuming and wasteful task when good vectors already exist. Since R factors do not occur in plant pathogens (only because antibiotics are not widely used to treat plant diseases), finding vectors with good selectable markers may be difficult. Furthermore, if self-cloning experiments are deregulated, there will not be the impetus to characterize and test the safety of these new vectors as thoroughly as those already certified in E. coli have been.

2) Self-cloning will not be possible in species which contain ubiquitous cyptic plasmids or are not transformable. In this case the DNA must be cloned into E. coli and the recombinant molecules reintroduced back into the host of orgin by transduction or conjugative mobilization. Such experiments are important and are not possible under present requirements for HV systems.

I wish to express my appreciation for the considerable effort that has already been given to adapting the guidelines to plant pathogens and I hope that you will give the above problems your further consideration.

Sincerely,

David L. Coplin

David L. Coplin
Assistant Professor

DLC:jlh

CC: E. Adelberg
A. Campell
P. Day
S. Falkow
W. Gartland
S. Gottesman
D. Helinski
R. Hornick
L. Jacobs
E. Kutter
J. Littlefield
J. Settlow
J. Spizizen
E. Redford
W. Rowe
D. Stetten
L. Walters
M. Zaitlin

Yale University *New Haven, Connecticut 06510*

SCHOOL OF MEDICINE
333 Cedar Street
Department of Human Genetics

April 21, 1978

To: Dr. Donald Frederickson

From: Edward A. Adelberg EAA

The enclosed letter deals only with "self-cloning" experiments in E. coli, but several Biohazard Committee Chairmen have noted that the same appeal should be made on behalf of all self-cloning experiments, such as B. subtilis genes in B. subtilis, etc.

EAA:bgf
Enclosure

Yale University *New Haven, Connecticut 06510*

SCHOOL OF MEDICINE
333 Cedar Street
Department of Human Genetics

April 21, 1978

Dr. Donald Frederickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

The proposed revised Guidelines for Recombinant DNA Research state: "In general, recombinant DNA molecules formed from any combination of DNAs will not be considered novel when all the components are derived from genomes known to replicate within the organism used to propagate the recombinant DNA." The revision also states: "These Guidelines...pertain only to novel DNAs."

If the above changes could be put into effect immediately, they would save the enormous amount of time and money now spent in processing M.U.A.s and inspecting laboratories in which the only relevant experiments involve the cloning of E. coli genes or coliphage genes in E. coli itself.

This is separate from the more complex matter of excluding recombinant DNAs that consist of segments of DNA from different species that are known to exchange chromosomal DNA by natural physiological processes. We understand that you now have a committee working on the list of "exchangers", and that this will take time. The matter of excluding "self-cloning", however, is quite straightforward and non-controversial; as chairpersons of Institutional Biohazards Committees we urge that, as soon as possible, you publish a directive excluding from the M.U.A. process all experiments in which segments of the E. coli chromosome, or of phages or plasmids that normally infect E. coli, are cloned by insertion into vectors that are then propagated in E. coli.

Respectfully,

Edward A. Adelberg
Professor of Human Genetics

EAA:bgf

On behalf of the Chairpersons of Institutional Biohazards Committees listed on the following page:

Dr. Michael J. Chamberlin
University of California
Berkeley, California

Dr. Arthur Riggs
City of Hope National Medical Center
Duarte, California

Dr. John Spizizen
Scripps Clinic & Research Foundation
La Jolla, California

Dr. Rose M. Litman
University of Colorado
Boulder, Colorado

Dr. Edward A. Adelberg
Yale University
New Haven, Connecticut

Dr. Philip I. Marcus
University of Connecticut
Storrs, Connecticut

Dr. Roger M. Herriott
Johns Hopkins University
Baltimore, Maryland

Dr. Bernard Fields
Harvard Medical School
Boston, Massachusetts

Dr. Daniel Branton
Harvard University
Cambridge, Massachusetts

Dr. Harlyn O. Halvorson
Brandeis University
Waltham, Massachusetts

Dr. Harry Stinson
Cornell University
Ithaca, New York

Dr. Arthur Bank
Columbia University
New York, New York

Dr. Frank E. Young
University of Rochester
Rochester, New York

Dr. Mary V. Hershfield
Duke University
Durham, North Carolina

Dr. Jonathan W. Uhr
Univ. of Texas Health Science Center
Dallas, Texas

THE J. HILLIS MILLER HEALTH CENTER
UNIVERSITY OF FLORIDA

Department of Biochemistry
and Molecular Biology

Phone: 904-392-3361
Gainesville, 32610

May 2, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have just sat through the April 27-28 meeting of the Recombinant Advisory Committee at the NIH. As a result of this meeting, and taking into account my experience on the University of Florida Institutional Biohazard Committee, I would like to offer several comments for your consideration when the Guidelines for Recombinant Research are revised by your office.

The main purpose of the Guidelines, to my mind, has been to make scientists think about their experimentation, not to insure safety per se. I regard most experiments as safe, as long as precautions are taken to insure proper disposal of all recombinant organisms. It is for this reason that I believe no experiments should be exempted from the Guidelines. If laboratory workers realize they are doing recombinant research, and realize there is a possible hazard, then I believe the spirit as well as the rules will be observed. By exempting experiments, usual laboratory procedure will be followed. Why cannot all recombinant experiments be carried out as P_1 experiments under the Guidelines, but review for many safe experiments be minimal or non-existent. I am opposed to blanket exemption from the Guidelines, and indeed I feel that just as radioisotope use is recorded, use of this technology, with its potential for permanent change of the environment, should be monitored.

I. Scientific Comments

A. A large class of experiments using recombinant DNA technology to transfer genetic information between various bacterial species have been exempted from the proposed Guidelines. On the basis of frequent transfer of chromosomal genes in nature, I agree that organisms listed in Tables 1 and 2 (see attached copy) present no unusual hazards. However, the extended Table 3, comprising essentially all of the gram negative bacteria, does not meet this criteria. All organisms in this table have been shown to transfer plasmids to E. coli; no information was given on the frequency of this event in nature, and no information was given on transfer between organisms other than E. coli. Considering the ecology of many of these bacteria, natural transfers of genetic information are probably nonexistent between many organisms in Table 3. Based on this concept, "probable natural genetic transfer", I would argue that organisms present in Table 3, not represented in Tables 1 and 2, should remain under the Guidelines, at P1 or P2 levels of containment.

EQUAL EMPLOYMENT OPPORTUNITY/AFFIRMATIVE ACTION EMPLOYER

B. Much discussion occurred in the Committee regarding the use of Saccharomyces cerevisiae as a cloning host. It was suggested that all such experiments be exempted from the Guidelines. I oppose this move. The point was carefully made that although genetic transfer out of S. cerevisiae does not exist, the yeast does survive. As a free-living, non-disabled organism, harmful products could be introduced into the environment -- for example, hormones or toxins. I would suggest that these experiments remain under the Guidelines, at the P1 or P2 level, until the development and certification of a disabled yeast strain with reduced natural survival meeting the criteria for HV-1 systems.

C. In general, I agree with the Animal Virus and EMBO Revisions for animal virus work. I would suggest that P1 NM (P1 no mouth pipetting) be made P2 -- there being no operational difference, and as stated above, I believe it would make the Guidelines more observed.

D. As a former bacterial geneticist, and presently as an animal virologist, I would concur with the reports of both the EMBO workshop and the Animal Virus Working Group and recommend that no mouth pipetting be allowed in P1, as well as P2-P4 containment. This is not a hardship to experimental protocol, using present devices.

II. Administrative Comments

A. Much of the flak you will catch will, I believe, come from exempting experiments from the Guidelines. I would suggest that all experiments involving recombinant technology be registered with NIH (through use of the checkoff box on grant applications and continuations) and with local IBCs. This registration need not be time consuming, but it would allow keeping track of who is doing what

B. If you truly expect these Guidelines to be respected, I would suggest that the ultimate penalty for violation be made identical to the penalties enforced for violations of the Human Experimentation Institutional Review Board.

C. Much of the responsibility for interpreting the Proposed Guidelines will rest with local IBCs. Would it be possible for the revision to explicitly state that the local IBC can refer to either the RAC or ORDA for advice or interpretation in complex cases.

Thank you for your consideration of my comments; you have my sympathy for what will be a scientifically difficult and politically impossible set of decisions.

Sincerely,

Philip J. Laipis, Ph.D.
Assistant Professor

PJL:sf

Attachment

The following organisms of the Enterobacteriaecae family exhibit chromosomal DNA relatedness (20% or more homology of DNA of various pairs tested) and genetic recombination or R-prime (R plasmid carrying chromosomal genes) transfer to E. coli K-12 mediated by the IncP-1 plasmids.

All species of the following genera:

1. Escherichia (including E. coli K-12)
2. Shigellae
3. Salmonella
4. Enterobacter
5. Arizona
6. Citrobacter
7. Klebsiellae

In addition the following species:

1. Erwinia amylovora
2. Erwinia dissolvens
3. Erwinia minipressuralis
4. Serratia marcescens
5. Levinea malonatica
6. Levinea amalonatica

The following organisms exhibit R-prime (R plasmid carrying chromosomal genes) transfer to E. coli K-12 mediated by the IncP-1 plasmids.

1. All members of the Enterobacteriaceae family
2. Vibrio species (excluding Vibrio parahemolyticus)
3. Pseudomonas species
4. Rhizobium species
5. Acinetobacter calcoaceticus
6. Agrobacterium tumafaciens
7. Rhodopseudomonas sphaeroides
8. Caulobacter crescentis

The following genera and/or species possess R plasmids (including R plasmids of the IncP-1 group) transferable to E. coli K-12.

1. All members of the Enterobacteriaceae family
2. Vibrio species (except Vibrio parahemolyticus)
3. Pseudomonas species
4. Rhizobium species
5. Acinetobacter calcoaceticus
6. Agrobacterium tumefaciens
7. Rhodopseudomonas sphaeroides
8. Caulobacter crescentis
9. Proteus species
10. Achromobacter species
11. Aeromonas salmonicida
12. Alcaligenes faecalis
13. Bordetella bronchiseptica
14. Myxococcus xanthus
15. Neisseria gonorrhoeae
16. Pastuerella hemolytica
17. Pastuerella multocida
18. Yersinia species
19. Xanthamonas sp.

In addition, recombinant DNA experiments between H. influenzae, H. parainfluenzae and H. ducreyi are exempt on the basis of extensive DNA homology.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 4 1978

OFFICE OF
RESEARCH AND DEVELOPMENT

Dr. Joseph G. Perpich
Associate Director for Program
Planning and Evaluation
Public Health Service
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Perpich:

The attached comments on the proposed revision to the Recombinant DNA Guidelines were prepared by Dr. Arthur Saz of my staff and are forwarded for your consideration.

Sincerely yours,

D. S. Barth

Delbert S. Barth, Ph.D.
Deputy Assistant Administrator
for Health and Ecological Effects

Enclosure-1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 1 1978

OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Proposed Revision to Recombinant DNA Guidelines

FROM: Arthur Saz, Ph.D.
Office of Health and Ecological Effects (RD-683)

TO: Delbert S. Barth, Ph.D.
Deputy Assistant Administrator for
Health and Ecological Effects (RD-683)

I have reviewed the proposed guidelines and my comments follow:

- Pages 2-3: Not necessarily relevant to Guidelines.

- Page 6: It would appear that the discussion on this page does not really refute the possibility that infectious particles could be produced in E. coli. It may not be necessary that viral gene products be formed precisely the same way in procaryotic and eucaryotic vectors. RNA splicing mechanisms are so recently reported that one cannot be certain that similar reactions do not occur in procaryotic vectors. Certainly endonucleolytic activity and ligation occur in procaryotes. Further, it has been demonstrated that translation can occur without capping. Discussion of inaccuracies of the expression of animal virus m-RNA in E. coli translation systems would appear to at variance with statements on page 3 indicating that in the future one may obtain large amounts of viral protein by gene cloning for use as vaccination agents. Here the translation system of the vector apparently would work adequately.

- Page 7: The evaluation of viruses to be adapted to replication in eucaryotic cells may not be

germane here as part of the evaluations at least may involve infectivity or penetrations. In the instance of a procaryotic vector, such a cell already has been "penetrated."

Further, it is not inconceivable that recombinant DNA-containing organisms sitting directly on mucosal cells of the intestine could penetrate directly into such cells and thus the nucleases in the intestinal contents would not be active. Direct penetration does not occur in bacterial enteritis.

o Table 1: I believe Sindbis and Semliki Forest viruses are positive-stranded RNA viruses, not negative-stranded as the table indicates.

I am in agreement that segmented genomes would probably cause no problems and with the recommendation on Baculoviruses.

In general, it would appear useful to do some experiments in an appropriate containment system to determine whether communicability is possible or probable.

These experiments should be performed prior to setting up the guidelines.

Other examples of a similar nature are scattered through the document and basically rest on the optimistic feeling that animal or plant viral replication will not occur in procaryotic vectors. It is probable that this is so but caution dictates the system should be tried first in phase 3 or 4 containment, however onerous or relatively expensive the chore.

cc: Dr. Armstrong, RD-683

The Connecticut Agricultural Experiment Station

123 HUNTINGTON STREET BOX 1106 NEW HAVEN, CONN. 06504 (203) 789-7258

Founded 1875 *Putting science to work for society*

10 May 1978

Gentlemen:

The attached letter from Dr. M.-D. Chilton and her colleagues outlines two recombinant DNA experiments that involve the plant pathogen Agrobacterium tumefaciens. The first is designed to assess risks and the second to assess potential agricultural benefits. These experiments are now prohibited by the current NIH Guidelines.

A recent workshop on agricultural pathogens recognized that there is natural exchange of chromosomal DNA between A. tumefaciens and E. coli K12 and agreed on reducing physical containment for intact plants as host-vector systems for recombinant DNA to P2. These recommendations were adopted by the Recombinant DNA Advisory Committee. The revised Guidelines now under study would therefore permit these experiments. However, several months are likely to pass before the revised Guidelines are adopted, and there is no assurance that they will be adopted in their present form.

I am therefore proposing that permission be given to carry out these experiments in the Plant Disease Research Laboratory, Frederick, Maryland. Dr. Emmett Barkley tells me that the secondary containment in this laboratory is equivalent to P4. It lacks glove boxes for primary containment but these are designed to protect workers from human pathogens and so would not usually be appropriate in a plant laboratory.

I believe that the information to be gained from these experiments will be useful and important for assessment of the risks and benefits to agriculture from recombinant DNA technology.

Sincerely,

Peter Day

Peter R. Day, Head
Department of Genetics

PRD/ebb
encl.

(1)Dr. J. Nielson, Acting Director
Science & Education Administration
USDA, Washington, D. C. 20250

(2)Dr. R. C. Atkinson, Director
NSF-Washington, D.C. 20550

(3)Dr. D.S. Fredrickson, Director
NIH, Bethesda, MD 20014

copies sent to:

Dr. E. Barkeley
Dr. Mary-Dell Chilton
Dr. Mary Clutter
Dr. W. Gartland
Dr. Clarence Grogan
Dr. M. Zaitlin

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

April 19, 1978

School of Medicine
Department of Microbiology and Immunology, SC-42

Dr. Mary Clutter
National Science Foundation
Washington, D. C.

Dear Mary:

There are two kinds of recombinant DNA experiments involving the Agrobacterium Ti plasmid that we would like to perform in a highly contained plant facility. We do not anticipate any danger to plants from the recombinant DNA. However because of the nature of the DNA molecules to be joined, one a conjugative broad host range plasmid and the other an oncogenic plasmid, the experiment would not be permitted under the present N.I.H. Guidelines. The two experiments we propose below can be viewed as: 1. Risk assessment, and 2. Benefit assessment. In the first, we propose to determine whether a "shrunken" Ti plasmid created by cloning can create a super-pathogenic bacterium. In the second, we propose to test whether such a "shrunken" Ti plasmid can be exploited as a vector to alter the nutritional quality of a crop plant.

Experiment 1. Creation of a shrunken Ti plasmid.

Agrobacterium Ti plasmids cause tumors in a wide range of dicotyledonous plants. The transformed plant cells, which can be propagated in vitro in the absence of the inciting bacterium, maintain one to several copies of a small segment of the Ti plasmid. It is not yet proven whether the Ti plasmid segment (T-DNA) is covalently joined to plant DNA. The length of the T-DNA is variable in different tumor lines.

We have cloned three Hind III fragments of Ti-B6-806 that encompass all or most of the T-DNA. The vector is PBR322, a vehicle that does not replicate in Agrobacterium so far as we can tell. The host bacterium is E. coli X1776. We have tested these clones for oncogenicity on carrot discs and the results were negative. In the laboratory of Jeff Schell in Gent, Belgium, a Ti::RP4 cointegrate plasmid has been transferred from Agrobacterium to a C600 strain of E. coli. While the cointegrate plasmid confers oncogenicity on the Agrobacterium host, the E. coli host does not acquire oncogenicity. Thus E. coli, even a robust strain, does not seem able to incite plant tumors, even though the entire Ti plasmid is present. In order to test small cloned fragments of the Ti plasmid for oncogenicity, it is therefore essential that they be transferred to Agrobacterium, the host in which the trait is expressed.

G305 Health Sciences Building / Telephone: (206) 543-5824

APR 26 1978

The fragments of the Ti plasmid to be tested must first be recloned in a vehicle that can replicate in Agrobacterium. The easiest choice would be to use RP4, which has a single Hind III site in the gene conferring resistance to kanamycin. The clones would be isolated by transforming into E. coli, and then transferred to Agrobacterium by conjugation. Conjugation of RP4 from E. coli to Agrobacterium occurs with high frequency (10^{-3}). The Agrobacterium strain would then be tested for oncogenicity on carrot discs and sunflower stemlets in vitro, and on tobacco and sunflower and kalanchoe plants in a high containment greenhouse.

If the small fragments of T-DNA presently available do not confer oncogenicity under the above conditions, we propose to clone larger sectors of the Ti plasmid by using partial digests. Using the colony-screening procedure in combination with Grunstein's colony hybridization technique, we can pick clones carrying segments of the Ti plasmid of any desired molecular weight that include the T-DNA. These recombinant DNAs would then similarly be moved to Agrobacterium for oncogenicity testing.

It seems virtually certain that a shrunken Ti plasmid can be created in this manner. The oncogenicity testing will reveal whether such a plasmid is more effective or less effective, whether its host range is altered, and whether its susceptibility to biological control by A. tumefaciens strain K84 is altered. In addition, the experiment would demonstrate the boundaries of the essential part of the Ti plasmid relating to tumor induction. This information would be useful to our studies of the mechanism of the process.

Experiment 2. Genetic Engineering with a shrunken Ti plasmid.

Because the T-DNA is maintained in plant cells, it can in principle be used as a vector to carry in nutritionally desirable traits. The system of choice for this experiment is Ti-T37, a plasmid that induces teratomas in tobacco. Dr. Armin Braun has demonstrated that cloned teratoma tissue can be induced to revert to a healthy plant of normal appearance. The plant nevertheless maintains copies of the foreign DNA, and expresses one tumorous trait, production of the amino acid derivative nopaline. Such a teratoma-plant would be a suitable test system for expression of foreign nutritional genes in the plant. Initial experiments could be done in tobacco, for which the methods are already known. Potato, a closely related solanaceous plant, should be amenable to the same kinds of manipulations.

The first step in the experiment is to create, by the methods outlined in Experiment 1 above, a shrunken Ti-T37 derivative.

The intact Ti-T37 plasmid could be used, but its large size would present potential problems for cloning. The foreign gene to be inserted into the T-DNA is chicken ovalbumin DNA, available as a clone in the laboratory of Dr. Savio Woo. The ovalbumin gene excised from this clone will be recloned into the shrunken Ti plasmid (E. coli host, selection for the ampicillin resistance of the RP4 component). Because the shrunken Ti plasmid will possess multiple cleavage sites for the cloning enzyme, a partial digest will be used. Subsequent screening by fingerprint analysis will reveal which clones have the ovalbumin DNA inserted into the T-DNA of the shrunken Ti plasmid. This recombinant DNA will be transferred to Agrobacterium by conjugation, and tumors will be incited on tobacco or potato plants in a high containment greenhouse. Tumor tissues will be put into tissue culture and can be tested for the presence of ovalbumin DNA, RNA transcripts from this DNA, and the protein (immunological assay). By Braun's grafting technique, teratoma plants will be obtained. We will attempt to propagate these vegetatively in order to obtain more experimental material. The resulting plants will be tested for production of ovalbumin or immunologically related protein, using various plant parts (especially the tubers, in the case of potato plants).

The advantages of the approach outlined above are several. We propose to use a eukaryotic gene, which should have the best chance of expression in the plant cell, for the engineering experiment. We do not require that an active enzyme be produced. The detection system is very sensitive, and should have low background. (We do not expect to find in normal plant tissue any protein serologically related to ovalbumin.) All of the steps in the experiment are feasible and appear to have a high probability of success. The only disadvantage of the experiment is that it involves recombinant DNA manipulations not allowed under the present N.I.H. Guidelines. This disadvantage could be overcome by working under conditions of high physical containment.

It has been pointed out by one member of our research group that the proposed experiment might be viewed as the creation of an egg-plant. Although it is stated with levity, this is indeed the purpose of the experiment. It is more promising to alter the nutritional quality of plant tissues by introducing genes coding for high quality storage protein than genes coding for synthesis of an amino acid. The amino acid is soluble, and thus is likely to be lost in cooking. In addition, expression of a foreign biosynthetic pathway in the plant promises to be a difficult process.

Sincerely yours,

Mary Dell Chilton

Eugene Nester

Milton B Gordon

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Medicine

15 May 1978

Donald S. Fredrickson, M.D.
Director, National Institutes of Health
Building 1, Room 124
Bethesda, MD 20014

Dear Don:

Bill Gartland has suggested that I write to you again about the section of the revised NIH recombinant DNA guidelines that relates to non-E. coli K12 host-vector systems.

I expressed my concern to you earlier (letter of November 9) about the wording of this section of the guidelines. Apparently, the matter was inadvertently omitted from the original agenda of the April advisory committee meeting and was again overlooked when the agenda for "late" items was compiled by Bill Gartland's office. So far as I am aware, the matter has still not been considered by the Committee.

My letter of April 14 outlines my concern: the authors of the section on non-E. coli K12 host-vector systems seem to have given little consideration to the development of such systems for purposes other than their possible use as alternatives to E. coli K12 for the cloning of genes of higher organisms. As I noted earlier, I believe that many of the practical benefits of recombinant DNA will depend on the ability to manipulate genes within organisms that produce medically important products such as antibiotics, or which carry out biologically important processes such as photosynthesis. The development of cloning systems in such species is of the greatest importance. Yet, so far as I can determine, the subject has only been considered in the most cursory way by the Advisory Committee. Consequently, the revised guidelines contain wording, which if allowed to stand, will literally preclude an entire area of experimentation that is of potentially great benefit and is widely accepted as posing little, if any, risk.

For example, as my earlier letter to you indicated, an experiment involving the introduction of genes from Streptomyces coelicolor into

Streptomyces lividans (which are non-exchangers) in order to design a more effective antibiotic, could not be done in the wild type antibiotic-producing strain at any level of physical containment whatsoever once the revised guidelines have gone into effect. The anachronism of prohibiting cloning of recombinant DNA molecules containing genes from these two non-pathogenic species is especially striking in view of recent changes in the very same guidelines that allow a wide variety of genes from infectious animal cell viruses to be introduced into E. coli K12 at sharply reduced levels of containment.

Surely, the committee could not have intended to prevent the experiments I have described above from being done at all. Yet, unless the wording of the proposed revised guidelines is modified by you, a whole class of experiments currently being carried out in entirely safe non-E. coli K12 systems will necessarily come to a halt in the United States when the new guidelines go into effect.

The changes in the definition of recombinant DNA in the revised guidelines do not appear to solve the problem. Moreover, in addition to precluding use of genetically unmodified non-pathogenic organisms as hosts, the guidelines' definition of an HV1 host-vector system as one that has "limited survival outside of the laboratory" is ambiguous. Does this mean all non-laboratory locations ranging from sewage to soil and air? What data would be required to demonstrate the limited survival outside of the laboratory of organisms such as Streptomyces and Pseudomonas? Would E. coli K12 continue to qualify as an "HV1 host" under the new definition? Certainly, limited survival outside the laboratory has not been demanded of E. coli K12 (or of yeast, for that matter) and it is not clear why this requirement is imposed for other organisms that are at least as non-pathogenic as E. coli K12.

The solution I propose is a modification of my earlier suggestion. The revised guidelines should simply state that "any bacterial species not known to be pathogenic to humans, to domestic animals or to agriculturally important plants may be used as an HV1 host-vector system". HV2 and HV3 host-fector systems would of course require certification by the Recombinant DNA Molecule Advisory Committee. Under this arrangement, non-E. coli K12 hosts could be used as recipients for DNA molecules that can be cloned at present in an EK1 host (i.e., those molecules which have been determined by the committee to present the lowest degree of risk). It seems to me that this proposal establishes a reasonable basis for the designation of non-E. coli K12 microorganisms as HV1 hosts.

Although only a limited number of investigators in the United States are presently working with non-E. coli K12 hosts as potential recipients

for recombinant DNA molecules, the recent development of transformation systems for Streptomyces (in David Hopwood's laboratory in England and in my laboratory), in photosynthetic pseudomonads, in Rhizobium, and in other organisms that make products of considerable biological or medical importance parallels the discovery made earlier this year in yeast, and these advances are changing the situation rapidly. Work in non-E. coli K12 organisms is proceeding at a rapid pace in Eastern and Western Europe; however, unless the wording of the proposed guidelines is changed, current work of great medical and social value will halt in the United States--simply because the drafters of this section of the revised guidelines did not, in my opinion, give thoughtful consideration to the implications of the wording. This matter is made worse because of the apparent administrative errors on two separate occasions, which kept discussion of this problem off the committee's agenda.

Don, if the system is going to work, the guidelines must have some internal consistency and rationality. I hope that you will see fit to modify the section dealing with HV1 hosts when you issue your final version of the revised guidelines. I would be glad to discuss the matter further with you or your staff by telephone if this would be useful to you.

With best regards,

Sincerely yours,

Stanley N. Cohen, M.D.
Professor of Medicine and
Professor of Genetics

Encls

cc: William J. Gartland, Jr.

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Medicine

14 April 1978

William J. Gartland, Jr., Ph.D.
Director, Office of Recombinant DNA Activities
National Institute of Health
Bethesda, MD 20014

Dear Bill:

In reviewing the material accompanying your memorandum of April 11 to the Recombinant DNA Advisory Committee, I noted that the proposal that I made earlier to Don Frederickson in connection with approval of non-E. coli host-vector systems has not been included for review by the committee. I have enclosed a copy of my letter of November 9 to Dr. Frederickson and I ask now that the Advisory Committee consider the following points at their upcoming meeting:

(1) Many of the practical benefits of recombinant DNA research will depend on the ability to manipulate genes within organisms that produce medically and biologically important products such as antibiotics.

(2) In revising the guidelines, the authors of the section on "other host vector systems" seem to have given little consideration to the importance of being able to manipulate the genes of such species per se, and have instead dealt with other host vector systems as an alternative to E. coli for cloning the genes of higher organisms.

(3) The revised guidelines state that cloning in host vector systems other than E. coli must use strains that have "low potential for survival in their natural environment" regardless of the lack of pathogenicity of the recipient species or the nature of the natural environment of that species. This appears to be a direct transfer, with little additional thought, of the considerations that pertain to the use of E. coli K12 for recombinant DNA experiments.

(4) In granting approval of Saccharomyces strains as recipients for cloned DNA, there was no requirement that the strains have "low potential

for survival in their natural environment". It appears inconsistent that the revised guidelines do not permit analogous use of non-pathogenic non-E. coli bacteria as hosts in experiments aimed at improving the quality or quantity of biological products made by those bacteria.

(5) For example, an experiment involving the introduction of genes by recombinant DNA methods from Streptomyces coelicolor to Streptomyces lividans in order to design a more effective antibiotic, could simply not be done in the wild type antibiotic-producing strain at any level of containment whatsoever. These organisms, although both closely related members of the genus Streptomyces, have not been shown to exchange DNA by natural physiological processes (although DNA can be exchanged by experimentally induced cell fusion). Since the wild type recipient (Streptomyces lividans) does not have a "low potential for survival in its natural environment" it could not be classified as an HV1 system. Thus, even though there would probably be unanimous agreement by scientists that the experiment I have described above poses virtually no risk whatsoever, the experiment could not be done, even under the highest levels of physical containment, under the proposed guidelines.

(6) By defining an HV1 system in this way, the authors of the revised guidelines have effectively included recombinant DNA experiments carried out in wild type non-E. coli hosts among the list of "prohibited experiments". Certainly, the Advisory Committee could not have intended to place a Streptomyces coelicolor-Streptomyces lividans recombinant DNA molecule on the "too dangerous to be made" list while at the same time permitting the cloning of DNA from a wide variety of animal cell and viral sources in E. coli K12 under minimal to moderate containment conditions. Yet, this is precisely the effect of the wording currently used in the revised guidelines.

(7) The problem can be resolved simply by having the guidelines state that "wild type isolates of any bacterial species not known to be pathogenic to humans, to domestic animals, or to agriculturally important plants may be used as an HV1 host type vector system provided that all components of any recombinant DNA molecules introduced into such a host vector system are derived from other prokaryotic organisms within Etiologic Agent Class 1. Use of a non-E. coli HV1 system for the propagation of DNA derived from organisms other than those included in the Etiologic Agent Class 1, or which are derived from eukaryotic organisms, shall be subject to certification as described in the guidelines". I believe this modification of

the wording will meet the committee's goals, while still enabling work of great importance and negligible hazard to proceed.

I hope that it will be possible for the Committee to consider this matter at its meeting later this month.

With best wishes,

Sincerely yours,

Stanley N. Cohen
Professor of Medicine and
Professor of Genetics

Encl

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Medicine

November 9, 1977

Donald S. Fredrickson, M.D.,
Director,
National Institute of Health
Building 1, Room 124
BETHESDA, Md. 20014

Dear Don:

I believe the proposed revisions of the NIH Guidelines on recombinant DNA research, as recently published in the Federal Register, represents a substantial improvement over the earlier version of the Guidelines. However, I do have a few comments and suggestions about the revisions.

(1) Definition of Recombinant DNA. There is an ambiguity in the proposed definition of "novel recombinant DNA." In order for a recombinant DNA molecule not to be considered novel, the Guidelines require that all of its components be derived from species that are known to exchange chromosomal DNA by natural physiological processes. This suggests that even if plasmids can be exchanged between two bacterial species by physiological processes, recombination of plasmid DNA segments in vitro is considered "novel" if exchange of chromosomal DNA has not also been demonstrated. However, further down in the same paragraph there is the statement that "all recombinant DNA molecules formed from any combination of DNAs will not be considered novel when all components are derived from genomes known to replicate within the organism used to propagate the recombinant DNA." This sentence implies that plasmid recombinants would not be considered novel if the plasmids can be exchanged, regardless of whether exchange of chromosomal DNA can occur. I think this apparent contradiction needs to be resolved.

My suggestion would be to define "novel recombinant DNAs" as follows: "molecules that consist of segments of any DNA from different species that are not known to exchange DNA by natural physiological processes." I know of no scientific basis for suggesting that organisms known to exchange extrachromosomal genetic information cannot also transfer chromosomal genes. Transduction and intracellular recombination between chromosomal and extrachromosomal DNA are well recognized biological processes.

The modification I suggest would remove any ambiguity and would eliminate the apparent contradiction with the statement contained later in the paragraph 1 of the "Introduction" section of the Guidelines.

(2) Other host vector systems. Many of the practical benefits of recombinant DNA will depend on the ability to manipulate genes within organisms that produce medically and biologically important products such as antibiotics. The development of cloning systems in such species is, in my opinion, of great value. Yet, in revising the guidelines, the authors of the section on "Other host vector systems" seem to have given little consideration to the importance of being able to manipulate the genes of such species per se, and have instead dealt with other host vector systems simply as possible alternatives to E. coli for the cloning of genes of higher organisms.

The revised guidelines state that cloning in host vector systems other than E. coli must use strains that have "low potential for survival in their natural environment," regardless of the lack of pathogenicity of the species or the nature of the natural environment of that species. This appears to be a direct transfer with little additional thought of considerations pertaining to the use of E. coli K12 for recombinant DNA experiments. I think it is important to recall that the "low survival" attributes of E. coli K12 were initially put forth as a response to those who had concerns about using a bacterial strain that they believed might inhabit the human intestine. At that time, critics proposed that only bacterial species unassociated ecologically with humans or with domestic animals should be used. Subsequently, data has been presented to indicate that E. coli K12 has little, if any ability to colonize the human gastrointestinal tract. Somehow, in the course of events, the argument that it is safe to use E. coli K12 as a host because it does not coloniz- the human intestine, has been distorted. The statement is now being made that E. coli K12 should be the only approved host, and that other bacterial species -- no matter how non-pathogenic and remote from human ecology -- must not be used unless it is specifically demonstrated that the recipients have a low potential for survival in their natural environment (whatever that environment may be).

I believe that this new requirement will seriously impede and perhaps entirely cripple work aimed at using a variety of non-pathogenic bacteria as hosts in experiments aimed at improving the quality or quantity of biological products made by those bacteria. For example, an experiment involving the introduction of genes by recombinant DNA methods from Streptomyces coelicolor to Streptomyces lividans, in order to design a more effective antibiotic, could simply not be done in the wild type antibiotic-producing strain at any level of containment whatsoever.

These two organisms, although both closely related members of the genus Streptomyces, have not been shown to exchange DNA by natural physiological processes, (although DNA can be exchanged by experimentally induced cell fusion) and gene exchange by in vitro methods would come under the NIH Guidelines. Since the wild type recipient strain Streptomyces lividans does not have "low potential for survival in its natural environment", it could not even be classified as an HV1 system. Thus, even though there would probably be unanimous agreement by scientists that the experiment I've described above poses virtually no risk whatsoever, the experiment could not be carried out, even under high levels of physical containment, under the proposed Guidelines. By defining an HV 1 system in an inappropriate way, the authors of the revised Guidelines effectively have included recombinant DNA experiments with wild type non-E.coli hosts in the list of "prohibited experiments". Certainly the advisory committee could not have intended to place a Streptomyces coelicolor-Streptomyces lividans recombinant DNA molecule on the "too dangerous to be done" list, while at the same time permitting the cloning of DNA from a wide variety of animal cell and viral sources in E. coli K12 under minimal to moderate containment conditions. Yet, this is precisely the inevitable effect of the wording currently used. I urgently ask that you resolve this serious inconsistency prior to approval of the revised Guidelines.

I suggest that the problem can be resolved by simply having the Guidelines state that "wild type isolets of any bacterial species not known to be pathogenic to humans, to domestic animals, or to agriculturally important plants may be used as an HV1 host-vector system, provided that all components of recombinant DNA molecules introduced into such a host vector system, are derived from other prokaryotic organisms within Etiologic Agent Class 1. Use of a non-E.coli HV system for the propagation of genes derived from organisms other than those included in Etiologic Agent Class 1, or which are derived from eukaryotic organisms, shall be subject to certification as described in the Guidelines."

I believe this modification will provide adequate safety while still enabling work of great importance and minimal hazard to proceed.

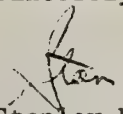
(3) Levels of biological and physical containment for certain experiments. In most instances, the investigator is given the option of using either P2 + EK2 containment or P3 + EK1. However, in the section dealing with shotgun experiments from mammals other than primates (page 49601 of the Federal Register, September 27, 1977), and in the experiments dealing with DNA from birds, there is no option of trading a higher level of physical containment for a lower level of biological containment. Depending on the gene to be cloned, there may be legitimate and compelling experimental reasons for an investigator to wish to use P3 + EK1 for such experiments, rather than P2 + EK2. For example, the approved EK2 host (or hosts) may not be suitable for detection of the gene to be cloned (e.g. the thy A mutation of X1776 prevents detection of expression of mammalian genes coding for the enzyme dihydrofolate reductase, since the host bacterial strain is already resistant to trimethoprim and methotrexate).

I believe that, for consistency, the Guidelines should give investigators the option to trade a level of physical containment for a level of biological containment in these categories, as they have done in others. If the principle of making such a trade is valid, it should be applied across the board.

(4) The institutional committee to be established in connection with recombinant DNA should be called an institutional biosafety committee, rather than a "biohazards" committee. It seems to me that the purpose of the institutional committee is to ensure the biosafety of recombinant DNA experimentation, whether or not biohazards are actually involved. Since the introductory section clearly points out that "to date, no known hazardous organism has been produced in this work," the term "biosafety committee" would seem to be more appropriate and would more accurately describe the responsibility of the committee. Continued use of the term "biohazards committee" helps to foster fears which,in my opinion, do not appear to be warranted.

I hope that these comments and suggestions will be useful to you and to the Advisory Committee in preparing the final version of the revised Recombinant DNA Guidelines.

Sincerely yours,



Stanley N. Cohen, M.D.
Professor of Medicine and
Professor of Genetics

SNC/jmd

Carnegie-Mellon University

Department of Engineering and Public Policy
Schenley Park
Pittsburgh, Pennsylvania 15213
[412] 578-2672

May 16, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

While I presently hold a visiting appointment in the Department of Engineering and Public Policy at Carnegie-Mellon University, my Ph.D. is in biochemistry. This past semester I taught a course which I entitled "Public Policy Issues in Biochemistry," which examined how some of the issues and techniques traditionally associated with biological research are coming increasingly into the realm of public policy issues. An obvious topic that we discussed in the course was recombinant DNA.

In preparing this section of the course, I reviewed a considerable portion of the literature, with an emphasis on risk evaluation and cost-benefit frameworks. My purpose in writing to you is to delineate some techniques and methods which might assist in future decision-making processes on this issue.

I read the proposed guideline revisions which appeared in the Federal Register (September 27, 1977) and I discussed them recently with Dr. Kamely in the Office of Recombinant DNA Activities. She indicated a significant problem with finalizing the revised guidelines is that the field is changing so rapidly that it is difficult to write a set of guidelines to cover all contingencies. A review of the literature would also suggest a considerable diversity of thoughts on the nature of appropriate guidelines.

Certainly the basic problem in assessing recombinant DNA activities is the uncertainty in the risk evaluation and the resulting subjectivity required in an evaluation of the proper containment for particular experiments. In addition, the series of events which might lead to an organism escape and environmental impact are probabilistic in nature. There appear to me a set of quantitative, analytical tools which would be useful, in a problem evaluation, depending on the nature of the question asked. For instance:

1. Is the combination of physical containment X and biological containment Y sufficient to reduce the probability of Z fatalities below probability P?

This type of question immediately suggests that a stochastic model of escape, establishment, and harmful consequences ought to be considered. It also begins to suggest that a series of uncertain events will have associated probability distribution of occurrences, and that someone is going to have to decide what an acceptable value of P is.

An alternative question is:

2. What set of guidelines can be developed with sufficient flexibility to encompass the fast-changing field of recombinant DNA?

This is a difficult question to evaluate, perhaps even more so than question 1, because there are no operational definitions for a number of words used in the question. First one would have to seek a resolution on terms like "sufficient," and also discover the parameters which describe the characteristics which are changing so rapidly.

Another question might be:

3. What is the escape risk from P1 through P4 facilities?

Dr. Roy Curtiss (Annual Review of Microbiology, 30: 507-533, 1976) attempts to answer this question, but the basis for his judgments is unclear.

Fault tree analysis, a techniques applied to systems, such as missles and airplanes, is an excellent quantitative tool for assessing the likelihood of failure modes of components which might lead to system failure. In this case, the system failure is "organism escape" and component failures might include fans and filters in air purification systems, or glove box leaks.

But a broader tool which would be applicable for questions 1 or 2 is decision analysis. It attempts to apply logical, mathematical and scientific procedures to decision problems which have the following characteristics: uniqueness, importance, uncertainty, long run implications and complex preferences. All of these characteristics appear in the recombinant DNA issue. Decision analysis is a systematic procedure to identify and define the decision, the decision-maker, the criteria for a "good" decision, and to evaluate the alternatives. It has been used in the past on such diverse problems as the decisions: 1) to seed hurricanes, 2) to provide adequate reserve for electric utilities, 3) to make corporate resource allocations, and 4) to plan wildfire protection in a mountain range.

The basic point is that there are several evaluation tools available which have not been applied to the recombinant DNA issue, but which if applied would systematize, discover and evaluate the important decision variables in the problem. Once the controlling variables are identified, and even if

significant disagreement still exists over their values, the range of issues will have been narrowed and focused for further discussion.

On another issues--the guidlines presently have a set of prohibited experiments such as the deliberate formation of recombinant DNAs containing genes for the biosynthesis of potent toxins. I realize that a P4 laboratory is being established at Fort Detrick to perform experiments thought to have among the greatest potential for hazard. However, has anyone considered the use of what might be a P5 or P6 lab--the Space Shuttle? I have not evaluated the economics, but NASA is looking for shuttle activites, and the probability of any organism escaping from a space craft to contaminate the earth environment would appear as close to zero as obtainable. The only group at risk would be the astronauts, who are already at high risk.

I urge you to consider analytical tools such as fault tree analysis or decision analysis for future decisions on recombinant DNA or other NIH activites. If you or others at the Institute are interested in pursuing analyses along any of these lines, I am certainly available to discuss them further.

Thank you for your attention.

Sincerely,

David Lincoln

David Lincoln
Visiting Assistant Professor,
Engineering and Public Policy

DL:em

72 Jane Street
New York N Y 10014
(212) 675-7173

Coalition for Responsible Genetic Research

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Solomon Garb M.D.
Membership Secretary

Francine R. Simring
Executive Director

June 1, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Fredrickson:

Attached hereto is a statement concerning the new proposed revisions for the Guidelines for Recombinant DNA Research.

This statement represents the position of the Coalition for Responsible Genetic Research as resolved at its meeting of May 7, 1978.

We trust that the recommendations included therein will be incorporated into further procedures of the NIH in time to ensure the required public participation.

Thank you for your kind consideration.

Yours very truly,

Francine R. Simring
Executive Director

FRS:fh

72 Jane Street
New York N Y 10014
(212) 675-7173

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Solomon Garb M.D.
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Francine R. Simring
Executive Director

STATEMENT ON NEW PROPOSED REVISIONS OF THE

RECOMBINANT DNA GUIDELINES

Whereas proposed new revisions for the Recombinant DNA Guidelines were approved at the meeting of the Recombinant DNA Advisory Committee, April 27-8, 1978, a public hearing to review the new revisions and a full Environmental Impact Statement are now in order.

The new revisions go far beyond the changes discussed at the public meeting held at the NIH, December 15-6, 1977. These proposed changes include the following:

1. Delegation of authority for initial approval of experiments from the NIH to local biohazards committees. (This would mean that experiments could be started before being reviewed by the NIH.
2. Exemption from the Guidelines of organisms known to possess an R-plasmid transferable to E. coli K-12. (This broad criterion would exempt such organisms as neisseria gonorrheae and vibrio cholerae. It was approved despite the fact that Dr. Stanley Falkow, the Committee's consultant on the ecology of microorganisms, dissented strongly from the majority view of the Committee.)

3. Reduction of containment for virus experiments to levels considerably lower than those in the Guidelines discussed at the December meeting.

The Committee also approved lowered containment levels for experiments aimed at attaining expression of rat growth hormone, rat pre- and pro-insulin, and rat insulin in E. coli. The levels approved were respectively P2 EK1, P2 EK1, and P2 EK2.

Approval was based on rule-of-thumb calculations carried out by the experimenters and one member of the Committee. Such rough conjectures as a basis for assessment violate the traditional canons of scientific procedure. This assessment and justification have all the more importance given that the experiments are being carried out with a view to future industrial applications.

In order that the foregoing information be given proper consideration and input, we respectfully request that adequate time be made available by prompt attention to these matters.

cc: Rogers, Ottinger
Kennedy, Stevenson
CEQ, EPA, OSHA

June 1, 1978:
Submitted to Dr. Fredrickson

UNIVERSITY OF COLORADO
MEDICAL CENTER
4200 EAST NINTH AVENUE
DENVER, COLORADO 80262
Box C-245

SCHOOL OF MEDICINE
DEPARTMENT OF PREVENTIVE MEDICINE
AND COMPREHENSIVE HEALTH CARE

7 June 1978

Dr. Donald Fredrickson
Director, NIH
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The new revisions of the Guidelines for Recombinant DNA Research should be reviewed at a public meeting similar to the one called in December for the previous revision. I feel that the public must be involved in the decision process since they are the ones whose health is at stake, in case the proposed guidelines were inadequate. For this reason, too, a full Environmental Impact Statement must be developed in regard to the new revisions.

Further, I think that authorization for experiments in this area should remain with the NIH, but regulation of laboratory procedures to protect employees and the public should be the business of OSHA and EPA respectively, not NIH.

Yours sincerely,

John C. Cobb, M.D., M.P.H.
Professor

JCC/rt

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72 Jane Street
New York N Y 10014
(212) 675-7173

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Solomon Garb M.D.
Membership Secretary

Francine R. Simring
Executive Director

June 19, 1978

Dr. Donald Fredrickson
Director
NIH
Bethesda, Md. 20014

Dear Dr. Fredrickson:

I am writing in response to your letter of June 5, which was received at our office on June 13.

Your comment that the Recombinant DNA Advisory Committee has primarily a scientific and technical responsiblity does not seem to me to answer to the requirements of the Federal Advisory Committee Act for a "balance of views"; nor to the need for expanded technical input from other disciplines such as medical microbiology, microbial ecology, epidemiology, etc. as mentioned in my previous letter concerning forthcoming Committee vacancies; nor indeed for the need to include representatives of those persons directly involved in the laboratory support systems: technicians, custodial personnel, et al.

It is not at all clear why the NIH has been so resistant to suggestions that are already in quite successful operation, for example, in Britain. The central advisory committee there, the Genetic Manipulation Advisory Group (GMAG), screens recombinant DNA projects, supervises research protocols, and advises and controls. GMAG is a broadly representative group which includes representatives of the public interest, trade unions, bu siness, and non-biologists, along with recombinant DNA specialists, safety officers from institutions involved in the research, et al. The primary responsiblity of this group is health and safety in the workplace.[1]

Your wise comment made at the December meeting that NIH would not want to regulate the research since its function is the promotion of the research might well provide an important key toward broadening the scope and view of the regulation of recombinant DNA activities. (GMAG regulates, but does not promote.) Alternative regulatory agencies such as OSHA and EPA might well be considered, as has been suggested from many sectors.

If we are to have valid public participation in the decision-making process, public representatives and

aforementioned others need to be part of technical committees. The invitation of these individuals to hearings called for at a point where they would have little effect on decision-making serves only to satisfy those outside the decision arena that their voices had been heard and at the same time would legitimize decisions already on the drawing board. [2]

New paths are never easy to break. We can understand the difficulties encountered by NIH in attempting to provide mechanisms for the new and still growing interface between science and society. But the importance of scientific responsibility to society is made clear almost daily as we read newspaper reports of once potential hazards of technology become real. And the public is making known its views on the funding of science.

It is our sincere hope that NIH and its expertise will bring to the ongoing issue of recombinant DNA activities the flexibility and integrity that are the hallmark of great science.

With all good wishes and the hope to hear your further views,

Sincerely yours,

Francine Robinson Simring
Executive Director

cc:
Cranston, Califano, Rogers,
Kennedy, Ottinger, Schweiker,
CEQ, OSHA, EPA, CDC

1. Williams Report of the Working Party on the Practice of Genetic Manipulation.

2. Molecular Politics in Britain and the United States: The Development of Policy for Recombinant DNA Technology, Dr. Susan Wright, University of Southern California Law Review.

FRS:fh

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

Program in Social Management & Technology

June 20, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am a member of the faculty of the above Program, teaching and doing research in the areas of technology assessment, technology and public policy, and the like. For the past year and a half, I have been a member of the University of Washington's Biohazards Committee which oversees research with recombinant DNA. During this time I have been very active in participating in the public policy discussions which have occurred about necessary forms of regulation for this research, appearing on radio and television programs, participating in a colloquium at the February meeting of the AAAS, and providing input into the staff of Senate and House committees working on proposed DNA legislation.

I am writing to you because of my concerns for both the procedure and substance of proposed revisions to the Guidelines for Recombinant DNA Research which were approved at the meeting of the Recombinant DNA Advisory Committee, April 27 and 28. I urge you to slow down the regulatory process so that adequate public consideration can be given to the proposed revisions.

In terms of process, I believe that the NIH has been remiss in consistently failing to follow the procedures required by the National Environmental Policy Act. A full impact statement should be developed and published on the proposed revisions. Adequate public hearings and other procedures to insure citizen input should be conducted.

As regards some of the substantive provisions of the revisions, I am concerned about the following items. At this time, I do not believe that sweeping delegation of authority for initial approval of experiments should be made from the NIH to local biohazard committees. The whole question of the most appropriate balance of authority between a central federal agency (which could assure that requisite technical and policy considerations are brought to bear on aspects of the guidelines) and local biohazard committees (which could assure sensitivity to local conditions and provide expanded means of public participation in the regulatory process) needs to be further developed. I have previously taken a position against sweeping federal preemption (as would have been provided by the bill authored by Representative Rogers); however, because many local biohazard committees do not yet provide

316 Guggenheim, FS-15 / Telephone: (206) 543-7029

a sufficiently open hearing and decision making process, within which local views can be adequately heard and considered. I do not believe that a dramatic delegation of authority is now warranted. I would prefer that the guidelines require that local biohazard committees be more representative of the interests in their local communities and require that meetings and decision making be more open and well publicized. If these reforms were adopted, then I would more readily support delegation of approval of experiments to them.

I am also concerned about the number of exemptions from the guidelines which have been proposed. I believe that the information on which these proposals are based is too uncertain; as you know, Dr. Stanley Falkow, of the University of Washington, has strongly objected to many of the suggestions.

In addition, the Recombinant DNA Advisory Committee has been repeatedly advocating reduction of containment levels for a variety of experiments. I am afraid that many of these suggestions do not rest on objective and scientifically verifiable factual bases. As a result, I do not believe that they should be implemented.

Thank you for this opportunity to express my views. I hope that your decisions, when made, are in accord with them. I would appreciate being personally informed of the decisions which you do make on these issues.

Very truly yours,

Philip L. Bereano
Associate Professor

PLB:rl

Carnegie-Mellon University

Department of Engineering and Public Policy
Schenley Park
Pittsburgh, Pennsylvania 15213
[412] 578-2672

June 28, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

In my letter of May 16th to you, I briefly described a set of analytical tools which would be useful for a systematic analysis of recombinant DNA activities. It was unclear to me in your response of May 30th whether or not you were presently funding such studies.

Is NIH presently supporting any intra- or extra-mural policy analysis of issues involving recombinant DNA activities? By this I do not mean actual laboratory studies, which I know NIH is supporting, but rather systems modeling and data synthesizing activities which would analyze the alternatives for public policy decision-making. The activities could include those I mentioned in my letter of May 16th. Alternatively, if you are receptive to proposals for policy analysis on this issue, I would be interested in developing a proposal to examine and synthesize the information using some of the tools briefly described in my earlier letter. If you do not have a funding program available for such studies, I would appreciate it if you could suggest a federal office or agency who would be receptive to such a proposal.

Thank you for your attention.

Sincerely,

David Lincoln

David Lincoln
Visiting Assistant Professor
Engineering and Public Policy

DEPARTMENT OF ZOOLOGY
UNIVERSITY OF GEORGIA
ATHENS, GEORGIA 30602

(404) 542-5469

July 11, 1978

Dr. Donald Frederickson, Director
National Institutes of Health
Bethesda, MD. 20014

Dear Dr. Frederickson:

I am writing to you in connection with the request that I made approximately one month ago to the Office of Recombinant DNA Activities, NIGMS that the red bread mold, Neurospora crassa be approved as a cloning vehicle in recombinant DNA experiments.

For your information I am enclosing a copy of the letter which was sent to Dr. Gartland to support that request. I might also note that several of my colleagues working with Neurospora have written supporting letters to Dr. Gartland. It is my understanding that my request was, in fact, approved by the Office of Recombinant DNA Activities, but that you vetoed this approval at this time and decided to defer action until completion of the revised guidelines. I hope you can understand that my colleagues and I are most unhappy with this action and the accompanying delay. We are most anxious to undertake experiments with Neurospora comparable to those which have already been done with yeast. In fact, as I point out in my letter to Dr. Gartland, we considered these experiments with Neurospora even before they were performed with yeast, but were not permitted to carry them out. Consequently, we are at an increasingly greater competitive disadvantage in exploiting these techniques to further the understanding of molecular mechanisms involved in genetic regulation in lower eucaryotes.

I can appreciate that you must be under considerable pressure from both proponents and opponents of recombinant DNA research. However, I felt I should write to indicate my unhappiness with your recent decision and to express the hope that you will do everything possible to expedite approval of experiments with Neurospora which are completely comparable to those with yeast; if anything, they are safer as I have indicated.

In conclusion, my colleagues and I hope you will make every effort to be consistent and fair in this matter. We are most unhappy with the forced delay in carrying out our experiments and trust that you will indeed expedite a reasonable resolution of this problem.

Sincerely yours,

Norman H. Giles

Norman H. Giles
Callaway Professor of Genetics

NHG/blq
Enc. 1

AN EQUAL OPPORTUNITY/AFFIRMATIVE ACTION INSTITUTION

DEPARTMENT OF ZOOLOGY
UNIVERSITY OF GEORGIA
ATHENS, GEORGIA 30602

(404) 542-5469

June 12, 1978

Dr. William J. Gartland
Director, Office of Recombinant
DNA Activities
NIGMS
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Gartland:

I am writing to you in connection with the utilization of the red bread mold Neurospora crassa as a cloning vehicle in recombinant DNA experiments.

Some months ago we were informed, on the basis of inquiries by the Chairman of our Bio-Hazards Committee here at the University of Georgia, Dr. Bruce Carlton, that such utilization was not permitted. This information came to Dr. Carlton on the basis of a telephone conversation he had with you.

Meanwhile, Dr. Gerald Fink at Cornell had similar ideas for using yeast in transformation experiments, and as I am sure you are aware, received permission from NSF, but initially not from NIH, to carry out such experiments. More recently this permission has been given by NIH. On the basis of these developments, I am raising once again the possibility of utilizing Neurospora crassa for similar experiments. We have been successful in inserting Neurospora DNA into the E. coli plasmid pBR322 with the subsequent expression of one of the genes in the qa gene cluster whose regulation we are interested in studying. This hybrid plasmid synthesizes in E. coli an enzyme, catabolic dehydroquinase, which is indistinguishable from the Neurospora enzyme and very different from the E. coli biosynthetic enzyme which it replaces. In our judgment these experiments constitute the first clear proof of expression with apparent complete fidelity at the levels of both transcription and translation of eucaryotic DNA in a procaryotic host. As I indicated, we have been interested for some time in doing the reverse experiment and introducing the recombinant DNA from E. coli into an appropriate Neurospora host as a test for transformation. The experiments which Dr. Fink has carried out have indicated that this can be done with yeast.

As I am sure you are aware, Neurospora species are Ascomycetes relatively closely related to yeast. Typically they occur in nature in tropical regions, often growning on burned-over sugar cane fields or on other dead vegetation. In the past Neurospora has been something of a pest in bakeries, hence the common name, red bread mold. In West Java, Neurospora is an essential component of ontjom, a foodstuff prepared from soybean or peanut cakes on which the fungus grows and conidiates. There is no evidence that this organism is in any way pathogenic to human beings, or indeed to any other animals. In fact, it must have been ingested on countless occasions without any health problems.

To my knowledge there is no evidence that Neurospora carries either DNA viruses or any structures comparable to bacterial plasmids. There is no evidence

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for any kind of genetic exchange between Neurospora and other fungi which are pathogenic. Gene exchange, either in experiments or in nature, is apparently confined to closely related species in the same genus, such as N. sitophila, N. intermedia, and N. tetrasperma.

Under these circumstances it seems to me that Neurospora would be a throughly suitable subject for recombinant DNA experiments with the same conditions applying as in the case of yeast, i.e., those conditions specified in the memorandum dated March 28, 1978 from Dr. Daphne Kamely of your office addressed to Institutional Biohazards Committees. In fact, Neurospora should be superior to yeast for such experiments since it is an obligate aerobe and unlike yeast, is incapable of growth in the human gut.

I would greatly appreciate your taking this request under advisement and would certainly hope that a prompt positive response will be possible. Naturally, we are anxious to pursue the experiments which have already been long delayed.

I am asking some of my colleagues working with Neurospora to write in support of this request. I hope you will let me know if there is any more information which you require at this time.

Sincerely yours,

Norman H. Giles
Callaway Professor of Genetics

NHG/blq

APPENDIX B

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95TH CONGRESS
2D SESSION

H. R. 11192

[Report No. 95-1005, Part I]

IN THE HOUSE OF REPRESENTATIVES

FEBRUARY 28, 1978

Mr. STAGGERS (for himself and Mr. ROGERS) introduced the following bill; which was referred to the Committee on Interstate and Foreign Commerce

MARCH 24, 1978

Reported (with amendments), sequentially referred to the Committee on Science and Technology for a period ending not later than April 21, 1978, for consideration of such provisions as fall within the jurisdiction of that committee under clause 1(r), rule X, and ordered to be printed

[Omit the part struck through and insert the part printed in italic]

A BILL

To extend for two years the scope of the containment requirements and the requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SHORT TITLE

SECTION 1. This Act may be cited as the "Recombinant DNA Act".

FINDINGS

SEC. 2. The Congress finds that—

(1) research and other activities involving recom-

binant DNA will improve the understanding of fundamental biological processes;

(2) the knowledge gained from such research and other activities may be of great benefit to medicine and agriculture and may provide many other benefits to society;

(3) while no hazard has been demonstrated, uncertainties exist regarding the extent to which organisms or viruses containing recombinant DNA may present a risk of injury to health or the environment, and there is a risk that any such potentially hazardous organisms or viruses may spread quickly and without warning to persons, agricultural plants and products, and other items in or affecting commerce;

(4) the public interest requires that until the uncertainties regarding the potential hazards of organisms and viruses containing recombinant DNA are resolved, the health and welfare of the population of the United States be protected from such hazards, and commerce in the United States is dependent upon such protection being provided; and

(5) to effectively accomplish such protection and consequently to effectively regulate commerce requires that any activity involving organisms or viruses con-

taining recombinant DNA (whether a research or commercial activity) be subject to control.

TITLE I—INTERIM REGULATION OF RECOMBINANT DNA ACTIVITIES

DEFINITIONS

SEC. 101. For purposes of this Act:

(1) The term "DNA" means deoxyribonucleic acid.

(2) The term "recombinant DNA" means DNA molecules which—

(A) ~~have been formed by joining together DNA segments in a cell free system~~ *are formed by joining together DNA segments outside of living cells* and which have the capacity to enter a cell and to replicate in such cell either autonomously or after they have become an integrated part of such cell's genome; or

(B) are the result of a replication of the DNA molecules described in subparagraph (A).

(3) The term "recombinant DNA activity" means the possession in a State of recombinant DNA by any individual or public or private entity and any activity (including research and transportation) undertaken in

a State by any individual or public or private entity for the production of recombinant DNA.

(4) The term "public entity" includes any Federal, State, or local governmental entity.

(5) The term "Secretary" means the Secretary of Health, Education, and Welfare.

EXTENSION OF THE RECOMBINANT DNA GUIDELINES

SEC. 102. (a) (1) Except as provided under subsection (b) and section 107(b)(2), during the period beginning on the tenth day after the date of the enactment of this Act and ending twenty-four months after such day, all recombinant DNA activities shall be carried out in accordance with—

(A) the requirements of sections II (entitled "Containment") and III (entitled "Experimental Guidelines") of the recombinant DNA research guidelines of the National Institutes of Health of the Department of Health, Education, and Welfare published in part II of the Federal Register for July 7, 1976;

(B) if such requirements are revised before the tenth day after the date of the enactment of this Act, such requirements as so revised and published in the Federal Register; or

(C) if such requirements are revised under paragraph (2), such requirements as so revised.

(2) The Secretary may, by regulation, amend in any manner any of the requirements in effect under paragraph (1) if he determines that the requirements in effect after such amendment will be sufficient for the protection of health and the environment. A regulation promulgated under this paragraph shall be promulgated in accordance with section 553 of title 5, United States Code.

(3) Before the expiration of the ten-day period beginning on the date of the enactment of this Act, the Secretary shall take such action as may be necessary to publicize and make available the requirements described in paragraph (1), including the publication of such requirements in the Federal Register.

(b) The Secretary may, by order, exempt, under such terms and conditions as the Secretary shall include in the order, from the requirements of subsection (a) (1) any recombinant DNA activity which the Secretary finds does not present a significant risk to health or the environment. Each such order shall be published in the Federal Register together with a statement of the basis for the order.

(c) (1) Each individual or entity which, on the *tenth day after the* date of the enactment of this Act, is responsible for the conduct of any recombinant DNA activity shall, in accordance with regulations promulgated under subsection

(d) and before the expiration of ~~ninety days from the date of the enactment of this Act~~ *ten days from the date such regulations first take effect under such subsection,* report in writing to the Secretary—

(A) such individual's or entity's name, and

(B) a description of such activity and an identification of the place or places in which it is being conducted, and

(C) assurances satisfactory to the Secretary that such activity will be carried out in accordance with the applicable requirements of subsection (a) (1).

(2) Each individual or entity which is to be responsible for a recombinant DNA activity to be commenced during the period described in subsection (a) (1) shall upon the commencement of such activity report in writing to the Secretary, *in accordance with regulations promulgated under subsection (d),* such individual's or entity's name, a description of such activity, an identification of the place or places in which such activity is to be conducted, and assurances satisfactory to the Secretary that such activity will be carried out in accordance with applicable requirements of subsection (a) (1).

(d) Before the expiration of the ninety-day period beginning on the date of the enactment of this Act, the Secretary shall issue proposed regulations for the administration of

the requirements of this section and section 105 and may include in such regulations provisions for reporting and for local entities to assist in the administration and enforcement of the requirements of subsection (a) (1). Such proposed regulations shall be promulgated without regard to section 553 of title 5, United States Code, and shall take effect upon their publication in the Federal Register. After such publication of such regulations the Secretary shall give interested persons an opportunity to submit written data, views, or arguments on such regulations and may provide opportunity for the oral presentation of views and arguments. After consideration of the relevant matter presented, the Secretary shall, by order, make such revisions in such regulations as he determines appropriate.

~~(c) The National Environmental Policy Act of 1969 shall not apply with respect to any action taken by the Secretary under this title.~~

PROHIBITED ACTS AND PENALTIES

SEC. 103. (a) No person may—

(1) conduct any recombinant DNA activity in violation of any applicable requirement of section 102;

(2) move in violation of an order issued under section 105 (c) any recombinant DNA or any other material subject to such order; or

(3) fail or refuse to—

(A) establish or maintain records,

(B) make reports or provide information, or

(C) permit entry or inspection,

as required by this ~~Act~~ *title* or any regulation promulgated under this ~~Act~~ *title*.

(b) (1) Any person who violates subsection (a) shall be liable to the United States for a civil penalty in an amount not to exceed $5,000 for each such violation. Each day such a violation continues shall, for purposes of this paragraph, constitute a separate violation of subsection (a).

(2) A civil penalty for a violation of subsection (a) shall be assessed by the Secretary by an order made on the record after opportunity (provided in accordance with this subsection) for a hearing in accordance with section 554 of title 5, United States Code. Before issuing such an order, the Secretary shall give to the person to be assessed a civil penalty under such order written notice of the Secretary's proposal to issue such order and provide such person an opportunity to request, within fifteen days of the date the notice is received by such person, such a hearing on the order.

(3) Any person who requested in accordance with paragraph (2) a hearing respecting the assessment of a civil penalty and who is aggrieved by an order assessing a civil penalty may file a petition for judicial review of such

order with the United States Court of Appeals for the District of Columbia Circuit or for any other circuit in which such person resides or transacts business. Such a petition may only be filed within the thirty-day period beginning on the date the order making such assessment was issued.

(4) If any person fails to pay an assessment of a civil penalty—

(A) after the order making the assessment has become a final order and if such person does not file a petition for judicial review of the order in accordance with paragraph (3), or

(B) after a court in an action brought under paragraph (3) has entered a final judgment in favor of the Secretary.

the Attorney General shall recover the amount assessed (plus interest at currently prevailing rates from the date of the expiration of the thirty-day period referred to in paragraph (3) or the date of such final judgment, as the case may be) in an action brought in any appropriate district court of the United States. In such action, the validity, amount, and appropriateness of such penalty shall not be subject to review.

(c) If the Secretary determines, after providing reasonable opportunity for an oral hearing, that a person has violated subsection (a) in carrying out a project for which

financial assistance was provided by a grant made under a program administered by the Secretary and from funds appropriated after the date of the enactment of this Act, the Secretary may, in his discretion, cancel such grant or withhold payments under such grant until he determines that such person will carry out such project in accordance with the applicable requirements of section 102.

INJUNCTION AUTHORITY; EMERGENCY PROCEDURE

SEC. 104. (a) The district courts of the United States shall have jurisdiction over civil actions to restrain any violation of section 103(a). Such a civil action may be brought in the United States district court for the judicial district where any act, omission, or transaction constituting a violation of section 103(a) occurred or wherein the defendant is found or transacts business. In any such civil action, process may be served on a defendant in any judicial district in which the defendant resides or may be found. Subpenas requiring attendance of witnesses in any such action may be served in any judicial district.

(b) The district courts of the United States shall have jurisdiction over any civil action brought (1) for the seizure or destruction of any recombinant DNA, or any material used in or produced by a recombinant DNA activity, which recombinant DNA or material was involved in a violation of section 103(a) or presents or may present a significant

risk to health or the environment or (2) for other appropriate relief to prevent its production or movement. Such civil action shall be brought in the district court of the United States within the jurisdiction in which such recombinant DNA or material is found.

INSPECTIONS

SEC. 105. (a) (1) For purposes of enforcement of the requirements of section 102, individuals designated as inspectors by the Secretary, upon presenting appropriate credentials and a written notice to the person in charge of the place to be inspected and after clearly informing him of their authority, are authorized to enter and inspect any place (including any vehicle or other conveyance which may be used in the transportation of recombinant DNA) in a State in which a recombinant DNA activity is being conducted or in which the inspector has reasonable grounds to believe such an activity is being conducted. A separate notice shall be given for each such inspection, but a separate notice shall not be required for each entry made during the period covered by the inspection. Such an inspection (A) shall be made during the normal business hours (if any) of the place being inspected and in a reasonable manner, and ~~(B)~~ *(B)* may extend to relevant equipment, materials, containers, records, files, papers, processes, controls~~, facilities, and all other things in the place~~ *and facilities* bearing on whether a recombinant

DNA activity is being conducted in accordance with the applicable requirements of section 102.

(2) Upon completion of any inspection authorized by paragraph (1) and prior to leaving the place inspected, the inspector shall give to the person in charge of such place a preliminary report which summarizes any condition or practice observed by the inspector which, in his judgment, indicates a violation of the requirements of section 102. The inspector shall also prepare a written final report of his findings and send it to such person within thirty days of the completion of the inspection.

(b) At the request of an inspector conducting an inspection under subsection (a), the person in charge of the place inspected shall provide such samples of—

(1) recombinant DNA in such place, or

(2) materials used in or produced by any recombinant DNA activity conducted in such place,

as the inspector may require to determine if the applicable requirements of section 102 are being complied with.

(c) If during an inspection conducted under subsection (a), recombinant DNA or any material used in or produced by a recombinant DNA activity which the inspector making the inspection has reason to believe is involved in a violation of section 103(a) or presents a sig-

nificant risk to health or the environment is found in the place inspected, such inspector may order the recombinant DNA or material detained (in accordance with regulations promulgated by the Secretary) for a reasonable period which may not exceed twenty days unless the Secretary determines that a period of detention greater than twenty days is required to institute an action under section 104(b), in which case the Secretary may authorize a detention period of not to exceed thirty days. Any recombinant DNA or material subject to a detention order issued under this subsection shall not be moved by any person from the place at which it is ordered detained until—

(1) released by the Secretary, or

(2) the expiration of the detention period applicable to such order,

whichever occurs first.

(d) No individual designated by the Secretary to conduct an inspection under subsection (a) shall be required to obtain a search or inspection warrant from any judicial officer before entering any place to conduct such inspection.

(e) No individual who is engaged in or has a direct financial interest in a project involving a recombinant DNA activity may be designated by the Secretary to conduct an inspection under subsection (a) of such project.

EFFECT ON STATE AND LOCAL REQUIREMENTS

SEC. 106. (a) Except as provided in subsection (b), no State or political subdivision of a State may establish or continue in effect any requirement for the regulation of recombinant DNA activities.

(b) Upon application of a State or political subdivision of a State, the Secretary shall, by order promulgated after providing (in accordance with this subsection) notice and opportunity for an oral hearing on such application and after considering local conditions, exempt from subsection (a) of this section, under such conditions as may be prescribed in such order, a requirement of such State or political subdivision applicable to recombinant DNA activities if—

(1) the requirement is the same as, or more stringent than, a requirement under section 102(a); and

(2) the requirement is necessary to protect health or the environment.

A State or political subdivision which submits an application under this subsection shall be given an opportunity for an oral hearing on such application to be commenced not later than sixty days from the date the application is submitted. The presiding officer at such a hearing shall upon conclusion of the hearing make a written recommendation to the Secretary respecting approval of the application upon which the hearing was held.

(c) Within—

(1) sixty days of the conclusion of a hearing held on an application submitted under subsection (b), or

(2) one hundred and twenty days of the date the application was submitted,

whichever occurs later, the Secretary shall either approve or disapprove such application. The decision of the Secretary shall be in writing, shall, if a hearing was held on the application, contain the recommendation made by the presiding officer at such hearing, and shall include a complete statement of the reasons for the decision of the Secretary.

TRAINING AND STUDIES

SEC. 107. (a) The Secretary may conduct and support training in the safe handling of recombinant DNA.

(b) (1) The Secretary shall conduct or support on a continuing basis studies designed to assess the risks to health and the environment which may be presented by recombinant DNA activities.

(2) The Secretary may, by order, make the requirements of section 102 inapplicable, under such terms and conditions as the Secretary shall include in the order, to any study conducted or supported under paragraph (1). Each such order shall be published in the Federal Register together with a statement of the basis for the order.

RELATIONSHIP TO OTHER FEDERAL LAWS

SEC. 108. (a) This title shall not affect the authority of any Executive agency (as that term is defined in section 105 of title 5, United States Code) to regulate under any other Act recombinant DNA activities.

(b) In exercising any authority under this title, the Secretary, or any person acting on behalf of the Secretary or pursuant to this title, shall not, for purposes of section 4(b)(1) of the Occupational Safety and Health Act of 1970, be deemed to be exercising statutory authority to prescribe or enforce standards or regulations affecting occupational safety and health.

TITLE II—COMMISSION FOR THE STUDY OF RESEARCH AND TECHNOLOGY INVOLVING GENETIC MANIPULATION

SEC. 201. (a) There is established a Commission for the Study of Research and Technology Involving Genetic Manipulation (hereinafter in this title referred to as the "Commission").

(b) (1) The Commission shall be composed of thirteen members appointed by the Secretary of Health, Education, and Welfare. The Secretary shall select members of the Commission from individuals distinguished in the fields of medicine, law, ethics, the biological, physical, and environ-

mental sciences, philosophy, humanities, health administration, government, and public affairs.

(2) (A) Except as provided in subparagraph (B), members of the Commission shall each be entitled to receive the daily equivalent of the annual rate of the basic pay in effect for grade GS–18 of the General Schedule for each day (including traveltime) during which they are engaged in the actual performance of the duties of the Commission.

(B) Members of the Commission who are full-time officers or employees of the United States shall receive no additional pay on account of their service on the Commission.

(C) While away from their homes or regular places of business in the performance of duties of the Commission, members of the Commission shall be allowed travel expenses, including per diem in lieu of subsistence, in the same manner as persons employed intermittently in the Government service are allowed expenses under section 5703 of title 5 of the United States Code.

(c) The Chairman of the Commission shall be selected by the members of the Commission from among their number.

(d) (1) The Commission may appoint and fix the pay of such staff personnel as it deems desirable. Such personnel

shall be appointed subject to the provisions of title 5, United States Code, governing appointments in the competitive service, and shall be paid in accordance with the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates.

(2) The Commission may procure temporary and intermittent services to the same extent as is authorized by section 3109(b) of title 5 of the United States Code, but at rates for individuals not to exceed the daily equivalent of the annual rate of basic pay in effect for grade GS-18 of the General Schedule.

SEC. 202. The Commission shall—

(1) conduct a study of Federal policy regarding activities involving the genetic modification of organisms and viruses and include in such study an evaluation of—

(A) the interim controls in effect under title I of this Act, actions taken to carry out and enforce such controls, and the need for an expansion of the scope of such controls;

(B) the effect of non-Federal requirements on recombinant DNA research and the necessity for preemption of such requirements by Federal requirements;

(C) federally sponsored programs to assess the

risk to health and the environment presented by recombinant DNA research; and

(D) federally sponsored basic and applied recombinant DNA research; and

(2) conduct a study of the long-term consequences of the development of a technology capable of accomplishing the genetic modification of organisms and viruses and include in such study—

(A) an evaluation of the anticipated applications of genetic manipulation technology to such areas as medicine, pharmacology, immunology, industrial fermentation, and agriculture; and

(B) a thorough consideration of the ethical, moral, social, economic, and political implications of the development and use of such technology.

SEC. 203. (a) The Commission shall in carrying out its duties under section 202 hold public hearings as appropriate.

(b) The Commission may secure directly from any department or agency of the United States information necessary to enable it to carry out its duties. Upon the request of the Chairman of the Commission, the head of such department or agency shall furnish such information to the Commission.

SEC. 204. (a) Not later than eighteen months after the date of the enactment of this Act, the Secretary shall report to the Congress the preliminary results of the evaluation being conducted under paragraph (1) of section 202.

(b) Not later than thirty months after the date of the enactment of this Act, the Commission shall (1) complete the studies prescribed by section 202, and (2) on the basis of such studies, make recommendations to the Congress, the President, and the appropriate Federal agencies regarding such Federal action as the Commission determines should be taken to promote, regulate, or review activities involving the genetic manipulation of organisms or viruses.

(c) The Commission shall terminate within sixty days of the date upon which it has carried out subsection ~~(a)~~ *(b)*.

95TH CONGRESS
2D SESSION

H. R. 11192

[Report No. 95–1005, Part I]

A BILL

To extend for two years the scope of the containment requirements and the requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation.

By Mr. STAGGERS and Mr. ROGERS

FEBRUARY 28, 1978

Referred to the Committee on Interstate and Foreign Commerce

MARCH 24, 1978

Reported (with amendments), sequentially referred to the Committee on Science and Technology for a period ending not later than April 21, 1978, for consideration of such provisions as fall within the jurisdiction of that committee under clause 1(r), rule X, and ordered to be printed

Purpose: **Calendar No. 334**

To extend National Institutes of Health guidelines to all research involving recombinant DNA and to establish a Commission to study such research.

Amdt. No. 1713

95TH CONGRESS
2D SESSION

S. 1217

IN THE SENATE OF THE UNITED STATES

MARCH 1 (legislative day, FEBRUARY 6), 1978
Ordered to lie on the table and to be printed

AMENDMENT

Intended to be proposed by Mr. KENNEDY to S. 1217, a bill to regulate activities involving recombinant deoxyribonucleic acid, viz: Strike all after the enacting clause and insert in lieu thereof the following:

SHORT TITLE

SECTION 1. This Act may be cited as the "Recombinant DNA Act of 1978".

FINDINGS

SEC. 2. The Congress finds that—

(a) research and other activities involving recombinant DNA will improve the understanding of fundamental biological processes;

(b) the knowledge gained from such research and other activities may be of great benefit to medicine and agriculture and may provide many other benefits to society;

(c) uncertainties exist regarding the extent to which organisms or viruses containing recombinant DNA may present a risk of injury to health or the environment, and there is a risk that any such potentially hazardous organisms or viruses may spread quickly and without warning to persons, agricultural plants and products, and other items in or affecting commerce;

(d) the public interest requires that until the uncertainties regarding the potential hazards of organisms and viruses containing recombinant DNA are resolved, the health and welfare of the population of the United States be protected from such hazards, and commerce in the United States is dependent upon such protection being provided; and

(e) to effectively accomplish such protection and consequently to effectively regulate commerce requires that any activity involving organisms or viruses containing recombinant DNA (whether a research or commercial activity) be subject to control.

TITLE I—INTERIM REGULATION OF RECOMBINANT DNA ACTIVITIES

DEFINITIONS

SEC. 101. For purposes of this Act:

(a) The term "DNA" means deoxyribonucleic acid.

(b) The term "recombinant DNA" means DNA molecules which—

(1) have been formed by joining together DNA segments in a cell-free system and which have the capacity to enter a cell and to replicate in such cell either autonomously or after they have become an integrated part of such cell's genome; or

(2) are the result of a replication of the DNA molecules described in subparagraph (1).

(c) The term "recombinant DNA activity" means the possession in a State of recombinant DNA by any individual or public or private entity and any activity (including research and transportation) undertaken in a State by any individual or public or private entity for the production of recombinant DNA.

(d) The term "entity" includes an individual, partnership, corporation, association, or public or private organization.

(e) The term "public entity" includes any Federal, State, or local government entity.

(f) The term "Secretary" means the Secretary of Health, Education, and Welfare.

(g) The terms "department or agency" and "department and agency" mean each authority of the Government of the United States, whether or not it is within or subject to review by another agency, but does not include—

(1) the Congress;

(2) the courts of the United States;

(3) the governments of the territories or possessions of the United States; and

(4) the government of the District of Columbia.

EXTENSION OF THE RECOMBINANT DNA GUIDELINES

SEC. 102. (a) (1) Except as provided under subsection (b) and section 106(b)(2), during the period beginning on the tenth day after the date of the enactment of this Act and ending twenty-four months after such day, all recombinant DNA activities shall be carried out in accordance with—

(A) the requirements of sections II (entitled "Containment") and III (entitled "Experimental Guidelines") of the recombinant DNA research guidelines of the National Institutes of Health of the Department of

Health, Education, and Welfare published in part II of the Federal Register for July 7, 1976;

(B) if such requirements are revised before the tenth day after the date of the enactment of this Act, such requirements as so revised and published in the Federal Register; or

(C) if such requirements are revised under paragraph (2), such requirements as so revised.

(2) The Secretary may, by regulation, amend in any manner any of the requirements in effect under paragraph (1) if he determines that the requirements in effect after such amendment will be sufficient for the protection of health and the environment. A regulation promulgated under this paragraph shall be promulgated in accordance with section 553 of title 5, United States Code.

(3) Before the expiration of the ten-day period beginning on the date of the enactment of this Act, the Secretary shall take such action as may be necessary to publicize and make available the requirements described in paragraph (1), including the publication of such requirements in the Federal Register.

(b) The Secretary may, by order, exempt, under such terms and conditions as the Secretary shall include in the order, from the requirements of subsection (a) (1) any re-

combinant DNA activity which the Secretary finds does not present a significant risk to health or the environment. Each such order shall be published in the Federal Register together with a statement of the basis for the order.

(c) (1) Each entity which, on the date of the enactment of this Act, is responsible for the conduct of any recombinant DNA activity shall, in accordance with regulations promulgated under subsection (d) and before the expiration of ninety days from the date of the enactment of this Act, report in writing to the Secretary—

(A) such entity's name, and

(B) a description of such activity and an identification of the place or places in which it is being conducted, and

(C) assurances satisfactory to the Secretary that such activity will be carried out in accordance with the applicable requirements of subsection (a) (1).

(2) Each entity which is to be responsible for a recombinant DNA activity to be commenced during the period described in subsection (a) (1) shall upon the commencement of such activity report in writing to the Secretary such entity's name, a description of such activity, an identification of the place or places in which such activity is to be conducted, and assurances satisfactory to the

Secretary that such activity will be carried out in accordance with applicable requirements of subsection (a) (1).

(d) Before the expiration of the ninety-day period beginning on the date of the enactment of this Act, the Secretary shall issue proposed regulations for the administration of the requirements of this section and section 105 and may include in such regulations provisions for reporting and for local public entities to assist in the administration and enforcement of the requirements of subsection (a) (1). Such proposed regulations shall be promulgated without regard to section 553 of title 5, United States Code, and shall take effect upon their publication in the Federal Register. After such publication of such regulations the Secretary shall give interested persons an opportunity to submit written data, views, or arguments on such regulations and may provide opportunity for the oral presentation of views and arguments. After consideration of the relevant matter presented, the Secretary shall, by order, make such revisions in such regulations as he determines appropriate.

PROHIBITED ACTS AND PENALTIES

SEC. 103. (a) No person may—

(1) conduct any recombinant DNA activity in violation of any applicable requirement of section 102;

(2) move, in violation of an order issued under

section 105(c), any recombinant DNA or any other material subject to such order; or

(3) fail or refuse to—

(A) establish or maintain records,

(B) make reports or provide information, or

(C) permit entry or inspection,

as required by this Act or any regulation promulgated under this Act.

(b) (1) Any person who violates subsection (a) shall be liable to the United States for a civil penalty in an amount not to exceed $5,000 for each such violation. Each day such a violation continues shall, for purposes of this paragraph, constitute a separate violation of subsection (a).

(2) A civil penalty for a violation of subsection (a) shall be assessed by the Secretary by an order made on the record after opportunity (provided in accordance with the last sentence of this paragraph) for a hearing in accordance with section 554 of title 5, United States Code. Before issuing such an order, the Secretary shall give to the person to be assessed a civil penalty under such order written notice of the Secretary's proposal to issue such order and provide such person an opportunity to request, within fifteen days of the date the notice is received by such person, such a hearing on the order.

(3) Any person who requested in accordance with

paragraph (2) a hearing respecting the assessment of a civil penalty and who is aggrieved by an order assessing a civil penalty may file a petition for judicial review of such order with the United States Court of Appeals for the District of Columbia Circuit or for any other circuit in which such person resides or transacts business. Such a petition may only be filed within the thirty-day period beginning on the date the order making such assessment was issued.

(4) If any person fails to pay an assessment of a civil penalty—

(A) after the order making the assessment has become a final order and if such person does not file a petition for judicial review of the order in accordance with paragraph (3), or

(B) after a court in an action brought under paragraph (3) has entered a final judgment in favor of the Secretary,

the Attorney General shall recover the amount assessed (plus interest at currently prevailing rates from the date of the expiration of the thirty-day period referred to in paragraph (3) or the date of such final judgment, as the case may be) in an action brought in any appropriate district court of the United States. In such action, the validity, amount, and appropriateness of such penalty shall not be subject to review.

(c) If the Secretary determines, after providing reasonable opportunity for an oral hearing, that a person has violated subsection (a) in carrying out a project for which financial assistance was provided by a grant made under a program administered by the Secretary and from funds appropriated after the date of the enactment of this Act, the Secretary may, in his discretion, cancel such grant or withhold payments under such grant until he determines that such person will carry out such project in accordance with the applicable requirements of section 102.

INJUNCTION AUTHORITY; EMERGENCY PROCEDURE

SEC. 104. (a) The district courts of the United States shall have jurisdiction over civil actions to restrain any violation of section 103 (a). Such a civil action may be brought in the United States district court for the judicial district wherein any act, omission, or transaction constituting a violation of section 103 (a) occurred or wherein the defendant is found or transacts business. In any such civil action, process may be served on a defendant in any judicial district in which the defendant resides or may be found. Subpenas requiring attendance of witnesses in any such action may be served in any judicial district.

(b) The district courts of the United States shall have jurisdiction over any civil action brought (1) for the seizure or destruction of any recombinant DNA, or any material used

in or produced by a recombinant DNA activity, which recombinant DNA or material was involved in a violation of section 103(a) or presents or may present a significant risk to health or the environment or (2) for other appropriate relief to prevent its production or movement. Such civil action shall be brought in the district court of the United States within the jurisdiction in which such recombinant DNA or material is found.

INSPECTIONS

SEC. 105. (a) (1) For purposes of enforcement of the requirements of section 102, individuals designated as inspectors by the Secretary, upon presenting appropriate credentials and a written notice to the person in charge of the place to be inspected and after clearly informing him of their authority, are authorized to enter and inspect any place (including any vehicle or other conveyance which may be used in the transportation of recombinant DNA) in a State in which a recombinant DNA activity is being conducted or in which the inspector has reasonable grounds to believe such an activity is being conducted. A separate notice shall be given for each such inspection, but a separate notice shall not be required for each entry made during the period covered by the inspection. Such an inspection (A) shall be made during the normal business hours (if any) of the place being inspected and in a reasonable manner, and (B)

may extend to relevant equipment, materials, containers, records, files, papers, processes, controls, facilities, and all other things in the place bearing on whether a recombinant DNA activity is being conducted in accordance with the applicable requirements of section 102.

(2) Upon completion of any inspection authorized by paragraph (1) and prior to leaving the place inspected, the inspector shall give to the person in charge of such place a preliminary report which summarizes any condition or practice observed by the inspector which, in his judgment, indicates a violation of the requirements of section 102. The inspector shall also prepare a written final report of his findings and send it to such person within thirty days of the completion of the inspection.

(b) At the request of an inspector conducting an inspection under subsection (a), the person in charge of the place inspected shall provide such samples of—

(1) recombinant DNA in such place, or

(2) materials used in or produced by any recombinant DNA activity conducted in such place,

as the inspector may require to determine if the applicable requirements of section 102 are being complied with.

(c) If during an inspection conducted under subsection (a), recombinant DNA or any material used in or produced

by a recombinant DNA activity which the inspector making the inspection has reason to believe is involved in a violation of section 103 (a) or presents a significant risk to health or the environment is found in the place inspected, such inspector may order the recombinant DNA or material detained (in accordance with regulations promulgated by the Secretary) for a reasonable period which may not exceed twenty days unless the Secretary determines that a period of detention greater than twenty days is required to institute an action under section 104 (b), in which case the Secretary may authorize a detention period of not to exceed thirty days. Any recombinant DNA or material subject to a detention order issued under this subsection shall not be moved by any person from the place at which it is ordered detained until—

(1) released by the Secretary, or

(2) the expiration of the detention period applicable to such order,

whichever occurs first.

(d) No individual designated by the Secretary to conduct an inspection under subsection (a) shall be required to obtain a search or inspection warrant from any judicial officer before entering any place to conduct such inspection.

(e) No individual who is engaged in or has a direct

financial interest in a project involving a recombinant DNA activity may be designated by the Secretary to conduct an inspection under subsection (a) of such project.

TRAINING AND STUDIES

SEC. 106. (a) The Secretary may conduct and support training in the safe handling of recombinant DNA.

(b) (1) The Secretary shall conduct or support on a continuing basis studies designed to assess the risks to health and the environmtnt which may be presented by recombinant DNA activities.

(2) The Secretary may, by order, make the requirements of section 102 inapplicable, under such terms and conditions as the Secretary shall include in the order, to any study conducted or supported under paragraph (1). Each such order shall be published in the Federal Register together with a statement of the basis for the order.

TITLE II—COMMISSION FOR THE STUDY OF RESEARCH AND TECHNOLOGY INVOLVING GENETIC MANIPULATION

SEC. 201. (a) There is established within the Department of Health, Education, and Welfare a Commission for the Study of Research and Technology Involving Genetic Manipulation (hereinafter in this title referred to as the "Commission").

(b) The Commission shall be composed of eleven mem-

bers. The Secretary shall, within sixty days from the date of enactment of this title, appoint—

(1) six members of the Commission from individuals—

(A) who are not and have never been professionally engaged in biological research,

(B) who are especially qualified to serve on the Commission as members of the general public by virtue of their training, experience, or background in the fields of medicine, law, ethics, education, physical, behavioral, and social sciences, philosophy, humanities, health administration, government, or public affairs, and

(C) who have no financial interest in recombinant DNA activities (not including wages or salary earned by an employee of a nonprofit educational or research corporation) ; and

(2) five (and not more than five) members of the Commission from individuals—

(A) who are or have been professionally engaged in biological research,

(B) who are especially qualified to serve on the Commission by virtue of their training, experience, or background, and

(C) who have no financial interest in recom-

binant DNA activities (not including wages or salary earned by an employee of a nonprofit educational or research corporation).

(c) The Chairman of the Commission shall be selected by the members of the Commission from among their number.

(d) Seven members of the Commission shall constitute a quorum for business, but a lesser number may conduct hearings.

(e) The Commission shall meet at the call of the Chairman or at the call of a majority of its members.

(f) Four or less vacancies on the Commission shall not affect the authority or activities of the Commission.

(g) (1) Except as provided in paragraph (2) members of the Commission shall receive compensation at a rate not to exceed for any day (including traveltime) the daily equivalent of the effective rate for GS–18 of the General Schedule while engaged in the actual performance of the duties vested in the Commission. While away from their homes or regular places of business in the performance of duties of the Commission, members of the Commission shall be allowed travel expenses, including per diem in lieu of subsistence, in the same manner as persons employed intermittently in the Government service are allowed expenses under section 5703(b) of title 5 of the United States Code.

(2) Members of the Commission who are full-time officers or employees of the United States shall receive no additional pay on account of their service on the Commission.

SEC. 202. The Commission shall conduct—

(a) (1) a study of the current state of knowledge of the dangers of recombinant DNA research including an evaluation of whether the Federal guidelines concerning such research are needed and, if needed, whether they are adequate;

(2) a study of the likely directions of recombinant DNA research in the future and the potential risks associated with such research; and

(3) a study of the appropriate role of the public in determining governmental policy concerning recombinant DNA research including a study of the appropriate roles of Federal, State, and local governments in assessing the risks associated with such research;

(b) a study of the long-term consequences of the development of a technology capable of accomplishing the genetic modification of organisms and viruses including in such study—

(1) an evaluation of the anticipated applications of genetic manipulation technology to such areas as medicine, pharmacology, immunology, industrial fermentation, and agriculture; and

(2) a thorough consideration of the ethical, moral, social, economic, and political implications of the development and use of such technology; and

(c) a study of the current and anticipated industrial applications of recombinant DNA research.

SEC. 203. (a) The Commission may for the purpose of carrying out its duties hold such hearings, sit and act at such times and places, take such testimony, and receive such evidence as the Commission deems advisable.

(b) The Commission may appoint and fix the pay of such staff personnel as it deems desirable. Such personnel shall be appointed subject to the provisions of title 5, United States Code, governing appointments in the competitive service, and shall be paid in accordance with the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates.

(c) The Commission may procure, in accordance with the provisions of section 3109 of title 5, United States Code, the temporary or intermittent services of experts or consultants. Persons so employed shall receive compensation at a rate to be fixed by the Commission, but not exceeding for any day (including traveltime) the daily equivalent of the effective rate for grade GS–18 of the General Schedule. While away from his home or regular place of business in the performance of services for the Commission, any such person

may be allowed travel expenses, including per diem in lieu of subsistence, as authorized by section 5703(b) of title 5, United States Code, for persons in the Government service employed intermittently.

(d) Upon the request of the Chairman or a majority of the members of the Commission, each department or agency shall furnish all information requested by the Commission which the Commission determines is necessary to enable it to carry out its duties and functions under this Act.

(e) The Commission, in performing its duties and functions under this title, may enter into contracts with appropriate public or nonprofit entities.

SEC. 204. (a) Not later than eighteen months after the date of enactment of this Act, the Secretary shall report to the Congress the preliminary results of the studies being conducted under subsection (a) of section 202.

(b) Not later than thirty months after the date of enactment of this Act, the Commission shall issue a report or reports on the studies set forth in section 202. The Commission shall simultaneously submit copies of such report or reports to the appropriate departments and agencies and to the appropriate committees of Congress. The Commission may, as it deems appropriate, include in such reports recommendations for administrative or legislative action.

(c) The Commission shall terminate within sixty days of the date upon which it has carried out subsection (b).

Amdt. No. 1713 Calendar No. 334

95TH CONGRESS
2D SESSION

S. 1217

AMENDMENT

Intended to be proposed by Mr. KENNEDY to S. 1217, a bill to regulate activities involving recombinant deoxyribonucleic acid.

MARCH 1 (legislative day, FEBRUARY 6), 1978
Ordered to lie on the table and to be printed

[COMMITTEE PRINT]

SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

REPORT

PREPARED BY THE

SUBCOMMITTEE ON
SCIENCE, RESEARCH AND TECHNOLOGY

OF THE

COMMITTEE ON
SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES
NINETY-FIFTH CONGRESS

SECOND SESSION

Serial X

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LETTER OF TRANSMITTAL

MARCH 1, 1978.

Hon. OLIN E. TEAGUE,
Chairman, Committee on Science and Technology, U.S. House of Representatives, Washington, D.C.

DEAR MR. CHAIRMAN: I am submitting herewith a Report on the Science Policy Implications of Recombinant DNA Research. The report is based on and provides a brief synthesis of the Subcommittee on Science, Research and Technology's hearings from March through September 1977. During that time the Subcommittee received comprehensive testimony from 50 witnesses. The witnesses assisted the Subcommittee in an examination of a broad range of issues including the status of the new recombinant DNA research in molecular biology and extending to the legal and ethical implications of this research for national science policy.

Although the primary objective of the hearings was to examine the significance for basic research policies of issues generated by the extremely high level of controversy over recombinant DNA research, the Subcommittee also heard, in correlation with this testimony, many comments with regard to several legislative proposals introduced during the first session of the 95th Congress.

A few comments on post-hearing developments are included so that Committee Members and others will be aware of recent topics considered significant in regard to the general findings contained herein. An earlier report of the subcommittee "Genetic Engineering, Human Genetics, and Cell Biology. Evolution of Technological Issues: DNA Recombinant Molecule Research" December 1976, provides background information.

The Subcommittee particularly wishes to acknowledge the assistance of Dr. James McCullough, Senior Life Scientist for the Science Policy Research Division, Congressional Research Service, and Dr. Gail Pesyna of the Committee Staff in the preparation of the report.

I believe this report and the hearings on which they are based are particularly timely, and contain much information which should be of great value in further considerations of this issue. I commend the report to you and to the other Members.

Sincerely yours,

RAY THORNTON,
Chairman, Subcommittee on Science, Research and Technology.

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SUMMARY OF CONCLUSIONS

(For complete text and discussion see pages 3–10)

In General

Immediate benefits of recombinant DNA research appear to be more imminent than the risks which have been hypothesized. . . .

Recombinant DNA research should continue to be supported in as positive and careful a fashion as possible. . . .

Since recombinant DNA research is underway in many nations, actions in the United States alone cannot be the final determining factor of the future of the research. . . .

There are clear instances of recognition of potential problems by private and commercial investigators with socially responsible actions resulting. . . .

The burden of proof of safety factors should not be borne exclusively by proponents of recombinant DNA research; opponents must assume a corresponding burden. . . .

Types of research currently permitted under recombinant DNA research guidelines do not seem to pose significantly greater risks than natural diseases routinely confronting the medical community; in many instances they appear to present less risk. . . .

NIH Guidelines for Recombinant DNA Research

The guidelines should be formalized by authorizing the extension of the NIH guidelines to regulate all recombinant DNA research for the present, recognizing that applicability of such guidelines to non-Federally funded research may require some restructuring. . . .

These guidelines should be evaluated continuously and kept consistent with new data. . . .

Better legal procedures for implementing the guidelines need to be developed. . . .

More attention should be given to improvement of procedures for public participation in developing guideline revisions. . . .

Before extending the guidelines to commercial institutions, further considerations should be given to special problems—such as protection of trade secrets and different regulatory approaches necessary in cases where large volumes of laboratory material must be used. . . .

Any legislative mandate providing recombinant DNA research regulations should contain a definite termination date of not more than 2 years from enactment, at which time the need for continuation of guidelines should be reexamined. . . .

The question of Federal preemption of State and/or local regulations of recombinant DNA research should be carefully considered and discussed with a view to avoiding balkanization of research before any decisions are put into law. . . .

Risk Benefit Factors

It is not presently possible to use traditional forms of risk-benefit assessment developed for other technological applications with regard to recombinant DNA research; for example, quantification of radioactive materials risks. . . .

Continuous recombinant DNA research risk-evaluation by researchers and monitoring by some formal public body appears necessary—particularly since various aspects of such research are limited due to ignorance of the biological processes involved. . . .

It seems probable that some "National Commission" should be established to assist in this process, but only to provide a forum for public inputs into future assessments—not to determine regulations. . . .

Implications for Science Policy

Information and education procedures at present seem inadequate, either for establishing social responsibility awareness by scientists or the understanding of scientific significance by the public. . . .

The professional societies could help a great deal in securing honest and open evaluation of subjects demanding scientific input and explanation. . . .

Congress should encourage scientific societies, insofar as feasible, to participate in programs of public education and community activities relevant to technical debates surrounding recombinant DNA and other research. . . .

Policy Processes and Procedures

All parties, government and non-government, need to maintain an awareness of the evolution of new methods, models, and institutions for resolving public issues, especially those in the private sector. . . .

The expansion of the perspectives provided by these institutions and their role in public education should be encouraged wherever feasible. . . .

While methods of public participation, scientific and nonscientific, have improved since the recombinant DNA issue first surfaced. other options and new resources looking toward better overall policy decisions must continue to be evaluated. . . .

Whenever legislative initiatives may be required to foster improved communication and coordination, Federal agencies should make such needs known as soon as possible. . . .

IX

International Considerations

In all deliberations regarding recombinant DNA research, the nature of its conduct and possible regulations thereof, American authorities must bear in mind that research in this area is going forward rapidly in other countries. . . .

Recombinant DNA research appears to have considerable potential for utility in many fields and hence may result in new technologies with marked economic impact. . . .

Any significant U.S. lag in genetic technology, for whatever reasons it may occur, could result in diminished power and prestige for this nation on the international scene. Such a possibility must not be overlooked as considerations for dealing with the recombinant DNA research issue go forward.

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ISSUES AND SCOPE OF THE HEARINGS

1. General Observations

Investigators in the field of cell biology now have isolated for laboratory research a series of enzymes which permit the researcher to rearrange with a high degree of precision the molecule containing the hereditary unit of the cell (the deoxyribonucleic acid, or DNA). The newly isolated enzymes permit the investigator to cut the DNA molecule at precise locations and to insert into the molecule new bits of DNA from other organisms. These newly formed genetic units, called DNA recombinant molecules, can then be inserted into a host cell, such as a bacterium, where they will multiply along with the regular host cell DNA during normal reproduction. This process is referred to as cloning the recombinant DNA molecule. Thus far, the most frequently used cloning cell has been the K–12 special variant of a bacterial species known as *Escherichia coli* although other host cells are available.

Since several other variants of *E. coli* are common in the human gut, there has been concern that recombinant DNA research might produce a pathogen which could become established in human beings. Another concern is that new organisms might be released into the environment and cause an ecological catastrophe. The potential for human engineering has been speculated upon as a futuristic type of problem of major social concern.

There was probably no development in basic research in 1977 which aroused more attention than the public debates on what to do about DNA recombinant molecule research. Although the recombinant DNA technique is basically a sophisticated research tool, the debates became polarized to such an extent that the ability of society to deal with new knowledge was called into question. Although it is difficult to separate all of the issues which are submerged in the recombinant DNA molecule research debates, the Subcommittee tried to consider such topics as:

> * * * demonstrated risks and benefits of DNA recombinant molecule research * * *
>
> * * * speculations concerning the potential threat to evolutionary processes as a result of interspecies transfer of genes * * *
>
> * * * need for continued regulation of DNA recombinant molecule research and the need for simliar controls over private and commercial research * * *
>
> * * * need for Federal regulation to protect the public health and safety from potential hazards from recombinant DNA research * * *
>
> * * * longer-range problems discussed in public debates over recombinant DNA research such as human genetic engineering * * *
>
> * * * the question of whether the recombinant DNA issue presents a serious confrontation between science and the law or science and politics * * *

* * * the degree to which appropriate groups were involved in the evaluation of the recombinant DNA issue * * *

* * * the impact on basic research scientists of the intense public scrutiny of recombinant DNA research * * *

* * * efforts at international coordination as a result of the DNA recombinant molecule research debates * * *

* * * the NIH DNA recombinant molecule research guidelines as a means for regulating basic research in this area * * *

* * * the probability that the NIH guidelines will be followed; the procedures for insuring compliance * * *

* * * the significance of the new concerns of local biohazards committees for basic research programs when Federal preemption appears to be warranted for the achievement of standard regulations * * *

* * * the significance of health and safety issues identified in recombinant DNA research issues with regard to other biomedical research subjects with some potential for hazard to the public health * * *

* * * alleviation of concerns for the public health without stifling basic research incentives * * *

* * * implications for trade secret protection, patent laws, and the protection of research grant proposals in the demand for increased public access to all phases of basic research planning * * *

* * * use of the patent process as a technique for regulating basic research * * *

* * * methodologies for dealing with risk-benefit assessments when data are incomplete or inadequate * * *

* * * the difficulty of the quantification of value judgments which are required for policy decisions * * *

* * * need for new institutional arrangements to facilitate public debate on value laden issues associated with basic research * * *

* * * increasing the effectiveness of representative government in dealing with public policy issues involving low probabilities of a very high consequence catastrophe * * *

* * * factors involved in developing science policies for short-, medium-, and long-range potential hazards * * *

* * * problems with current risk-benefit assessments which preclude the use of traditional methods for evaluation of issues involving a high content of value and ethical decisions * * *

* * * the appropriate role for the Congress in debates which involve ethics and values affecting the determination of research priorities * * *

* * * maintaining the right to freedom of inquiry while providing for the right of the public to protect itself against potential hazards from basic research * * *

* * * the constitutionality of the right to restrict research on the basis of conjectured hazards * * *

* * * the basis of the concern of some scientists that proposed regulation of recombinant DNA research represents a threat to freedom of inquiry * * *

* * * the question of who should be involved in the determination of research priorities for specific research * * *

* * * whether the accumulation of knowledge should be restricted because of the potential misuse which might be permitted by an uncontrolled society * * *

* * * the possibility that there might be realms of knowledge into which mankind should not stray * * *

* * * ways in which the Congress can facilitate communication between science and society for the improvement of human welfare * * *

* * * roles of scientific societies in aiding in policy determinations * * *

* * * the value of existing educational systems in providing an adequate preparation of scientists and non-scientists to participate in public policy issues * * *

* * * adequacy of "public" representation in debates concerning research issues affecting health and safety * * *

* * * need for new institutional procedures for the evaluation of public fears about the long-range social implications of basic research * * *

* * * need for reevaluation of the processes for allocation of resources for research * * *

* * * the fundamental basis for the societal anxieties about scientific research * * *

* * * whether public speculation about risks can ever be reconciled with scientific experimental data and experience * * *

* * * the basis of the increasing challenges to scientific integrity * * *

* * * need for processes for setting policy to insure that adequate notification of new developments is provided to the public * * *

* * * improvement of communication from the scientific community to the public on controversial matters with a high technical content * * *

* * * policy considerations from the larger philosophical questions of the use and abuse of knowledge * * *

The subcommittee heard many penetrating discussions which touched upon these and related issues. It became obvious that there is no simple answer to any of these problems. However, it is possible to consider some general observations and conclusions from the extensive hearings. The summary report herein should be reviewed for a more detailed discussion of these points. The hearings provide complete testimony and supplementary materials.

2. Conclusions

A. DNA RECOMBINANT MOLECULE RESEARCH

This technique is expanding in scope and appears to be of significant value in basic research as a tool for elucidating the nature and function of the genetic apparatus. Immediate benefits appear to be

more imminent than risks which have been hypothesized although there are so few data available at this time that no absolute conclusions can be derived. In any event, the research and its evolving technologies are not limited to the United States and thus actions in this Nation alone cannot be the final determining factor. The impact, whether beneficial or harmful, will be worldwide in nature and will require continuous cooperation and evaluation at an international level. A good start at such an international exchange of information and cooperation appears to have been initiated.

The Subcommittee concludes that the research should continue to be supported in as positive a fashion as is possible. The current high level of communication and vigilance between scientists and lay persons should be maintained. Despite the strong tone of the criticism of scientists conducting this research (however, see also the section of this report which refers to post-hearing developments), there are clear instances of a recognition of potential problems and socially responsible actions have been taken by both private and commercial investigators. For example, an investigator in a commercial laboratory who had developed a special cellulase-containing form of *E. coli* (by non-recombinant DNA methods) which might have had a commercial value did not pursue this lead because of a perception of potential environmental risk. In other research, the construction of an hybrid between a tumor virus (SV40) and an adenovirus (a cold causing virus) as a useful tool for mapping gene structure was offered for research use only under safety agreements; a proposed insertion of the SV40 tumor virus into *E. coli* for study of the virus structure was not completed because of a perception of potential risk and actually was one of the proposed experiments which led to the scientific evaluation of the potential risks of recombinant DNA research and the development of the NIH guidelines.

The Subcommittee does not believe that the burden of proof of safety should be borne only by the proponents of this area of investigation. In the absence of proof to the contrary, the right of freedom of inquiry is so important in our society that great care needs to be taken in any proposed restrictions of this freedom. However, opponents of research should have an equal opportunity in grant proposals to initiate research to attempt to develop data to evaluate their speculations of unusual risks.

The Subcommittee recognizes that all research is not automatically protected and that there are precedents for restriction of research. For example, national support of offensive biological warfare research was terminated when international negotiations led to a decision to outlaw such activities. Many categories of human experimentation are very carefully regulated in this country. Other forms of control, such as required licensing for the use of radioisotopes in research, have been imposed. However, the biomedical community has an excellent record of reacting to and coping with unexpected dangers. The investigations of pathogens "from the streets of Philadelphia to the villages of southern Sudan and northern Zaire" (Legionnaires disease, and the highly infectious and lethal African hemorrhagic, Lassa, and Marburg fevers) in recent times are evidence of the scope of successful albeit very risky research of great social value. These, and new forms of old

diseases such as the evolution of antibiotic resistant bacteria, are continuing evidence of the natural processes at work in nature which threaten mankind. On the basis of the available evidence, the types of research currently permitted under the recombinant DNA research guidelines do not seem to pose significantly greater risks than natural diseases constantly confronting epidemiologists and pathologists all over the world and in many instances appear to present less risk. On balance, the biomedical research community has a highly credible record of safety although continual improvement in safety standards must be required.

B. THE NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

The guidelines appear to be the product of a conscientious effort to insure the use of adequate physical and biological safeguards to protect the public health. There is a need to evaluate these guidelines continuously and insure that they are kept consistent with new data. Further, there appears to be a need to give more care to the legal procedures for implementation of the guidelines. This is particularly true since the Director of the National Institutes of Health has no desire or the manpower to play the role of a regulatory agency although the implementation of the guidelines will require some action of this nature. More attention needs to be given to improvement of the procedures for public participation in the development of revisions of the guidelines. Such participation should include a broader spectrum of scientific disciplines as well as ample and timely opportunities for public interest groups to make known their concerns and alternative options.

The Subcommittee concludes that legislation should be adopted authorizing the extension of the NIH guidelines to regulate all recombinant DNA research—Federal, State, private or commercial. The extension of the guidelines to non-federally funded research and to commercial development and production using recombinant DNA techniques may require restructuring of the Guidelines for two distinct purposes: (1) the regulation of any research involving the use of this technique and (2) the regulation of commercial production utilizing the DNA recombinant molecule technique.

The Subcommittee believes that there are special problems which require further consideration before the Guidelines can be extended to commercial institutions. The protection of trade secrets and the granting of patents are of particular concern not only in this Nation but abroad. In Great Britain, for example, where commercial interest is very strong, confidentiality is one of the most difficult issues which is currently confronting the Genetic Manipulation Advisory Group set up to review the use of this technique in genetics. Similar concern has been voiced in this country as evidenced by the testimony received by the Subcommittee. This problem will require resolution if the public review required to assure safety and compliance is to be reconciled with the trade secret and patent protection needed to foster favorable applications of the DNA recombinant molecule technique. Other obvious problems requiring attention in order to extend legisla-

tion to commercial firms include, but are not limited to, the need to work with greater volumes of material and avoiding unnecessary dupplication or overlap with existing statutes such as the Toxic Substances Control Act, the Federal Food, Drug, and Cosmetic Act and the Public Health Services Act.

The Subcommittee believes that legislation to authorize the extension of the Guidelines for Research Involving Recombinant DNA Molecules should have a definite termination date, perhaps after a period of two years, and that the need to continue such regulation should then be reexamined. There are important constitutional issues of freedom of inquiry which must be carefully considered if scientific research is not to be suppressed. The determination of the need to regulate and how to conduct such regulating is not always clear, and hasty, ill-conceived legislation may produce more harm than good to the spirit of free inquiry. There is no question that there is a need for Government to protect society when there is a clear threat to that society. However, the determination of this threat is not always an easy task and this is the case in the evaluation of the risk from recombinant DNA research. Science is a dynamic process; the public often tends to want to "fix" the response permanently. It becomes a difficult matter to construct controls sufficiently flexible to provide a protective response which can be modified easily as definitions of risk become clearer.

The Subcommittee concludes that the issue of whether Federal preemption should be included in any legislation which may be enacted to regulate recombinant DNA research requires careful consideration. While Federal regulations for the conduct of research generally should apply in order to insure a national standard of conduct, and hopefully similar international criteria, State and local communities have shown that valuable contributions can be made when citizens are adequately informed and interested. Procedures need to be established whereby States and local communities can provide this type of input and can even seek standards higher than those set nationally under special circumstances. The involvement of local communities could be assured in a number of ways, but broad participation on joint representative committees, such as bio-hazards committees holding frequent open hearings, have proven to be useful forums for allaying public fears about new and complex issues in science. Perhaps local citizens participating in biohazard committees monitoring and enforcing actions required by Federal legislation could assist in identifying the need for revision of the Federal Guidelines and associated legislation.

C. RISK-BENEFIT ASSESSMENTS

Risk-benefit assessments are not a need peculiar to recombinant DNA research. However, it is obvious that it is not possible at the present time to use traditional forms of risk-benefit assessment which have evolved for other technological applications where quantification of the risk, as with radioactive materials, is more readily achieved. The evaluation of the future social impact of recombinant DNA research is particularly difficult to accomplish because of the many intangible factors requiring consideration. Estimates of benefit-risk are frequently based upon speculation and such discus-

sions involve highly complex value judgments. Great progress has been made in collecting information and data which supports a reduction in the degree of risk being perceived for most of the DNA recombinant research being conducted. There is still a need for further and continuing evaluation of this area since certain types of research are still prohibited or severely limited because of ignorance of the biological processes involved. Under the circumstances, continuous monitoring of recombinant DNA research by a formal public body appears to be necessary, with opportunities being provided for regular reassessment of the status of any judgments as research and evolving technologies provide more data. Such reassessments also will continue to require policy evaluations in which scientists should participate but on which representative forms of Government should make the final decisions.

Because of the tenuous nature of the assessments of risks and benefits and the high level of public interest in and concern about this new research technique, the Subcommittee recommends that a "National Commission" be established to provide a forum for public assessment of the evidence pertinent to this issue. Such commissions have served very useful functions in the resolution of other societal conflicts in areas, for example, like fetal research, human experimentation, and psychosurgery. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research received favorable comments during the Subcommittee's hearings as a model of the type of forum within which issues of high technical content with conflicting views of social and scientific value may be examined. A similar commission to provide for a public review process during the period of temporary regulation of recombinant DNA research could serve a useful function by evaluating the need for continuation of regulation and the form which such regulation could take. All concerned segments of the public should be represented or provided with ample opportunity to present their views. Such a national commission could be charged to report its findings to the Congress as appropriate as well as to the agencies with responsibilities assigned under temporary recombinant DNA regulation legislation.

D. GENERAL IMPLICATIONS FOR SCIENCE POLICY

Current educational procedures do not appear to be adequate, either for increasing an awareness of social responsibility on the part of scientists, or an awareness of the meaning of scientific developments on the part of public policy groups. The examination of such issues should be public with adequate opportunity for free participation by affected public groups—both research and public interest groups. This may require a special effort to encourage scientists to become involved since the recombinant DNA experience has shown again that scientists who do get involved often are subjected to criticism by their peers and must expend a considerable amount of time explaining not only the basis for their original concern but also their changing perceptions as new data are made available.

As noted by several of the witnesses who testified before the Subcommittee, this process of formalizing the examination of the "contract between science and society" has been only sporadic within the

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universities. Further, in some instances, discussions of the ethics of science as a specific topic within a formal curriculum is frequently limited to professional fields such as medicine, law or engineering. The concern of many of the witnesses was that these discussions of the expanding role of the scientific community in interactions with the informed lay citizen may require a special effort to reach all students in every field of study.

The professional societies could do much more to aid in securing honest and open evaluation of subjects requiring scientific input. A few of the professional societies are moving in this direction. The American Association for the Advancement of Science, for example, provided the Subcommittee with introductory information about its Committee on Scientific Freedom and Responsibility in which it is examining the problems of self-regulation within scientific research.

The Subcommittee also concludes that this Subcommittee and the Congress generally should continue to encourage scientific societies, within the limits of Federal law, to participate in programs of public education and community activities which will assist the public in evaluating both sides of highly technical debates. The success of local key citizens recombinant DNA committees in evaluating and understanding the research issues clearly demonstrates that the public can understand and reach reasonable decisions on complex issues when scientists participate in such open discussions. The scientific societies and other formal institutions could do much to anticipate such problems and provide more opportunities in support of public seminars for discussion of evolving research with public policy implications before controversies become highly polarized.

E. PROCESSES AND PROCEDURES FOR SETTING POLICY

A number of experimental models for securing public involvement in science policy determinations have evolved in the United States and in other countries. Testimony before the Subcommittee provides more detail about some of these experiments. Such models should continue to be examined and tested. Some, like the National Commission for the Protection of Human Subjects mentioned earlier, have served both to alleviate public anxiety and to improve the environment in which specific types of scientific experiments can be conducted with social approval.

There is a need for the Congress to maintain an awareness of the evolution of these several new models for resolving public issues, especially those in the private sector.

The Subcommittee also has been made aware of the evolution of specific academic institutions such as the Institute of Society, Ethics, and the Life Sciences, Hastings-on-Hudson, New York; the Center for Bioethics, Georgetown University; also the National Endowment for the Humanities and the Assembly of Social and Behavioral Sciences of the National Academy of Sciences.

The Subcommittee concludes that the need for developing principles and methodologies for clarifying ethical issues affecting research is being noted by such institutions as an important public need for crystallizing basic ethical options. The expansion of the perspectives provided by these institutions and their role in public education should

be encouraged wherever appropriate. The addition of a procedural approach for the examination of ethical values correlated with scientific data should significantly improve the task of insuring public accountability discussions involving research issues. There may even be additional need at the Federal level for formalizing other institutional processes to foster such public sessions.

The Subcommittee also concludes that the manner in which public interest groups and private citizens, both scientific and non-scientific, have participated in policy decisions has improved since the first identification of a potential hazard in recombinant DNA research by the scientists themselves. However, other options should continue to be evaluated not only to further improve the existing processes but also to use the new resources and institutions which are becoming available for the study of such issues. The DNA recombinant molecule research issue is a valuable case history of the science-society conflict which has been evolving since the initiation of the "consumer protection" and "environmentalist" movements in the 1960's. The lessons available should be used to alleviate further acrimonious and unproductive debate and to construct an environment in which open public examination prevents unnecessary anxiety, provides for an optimum freedom of inquiry, and protects the public health and the environment. If these lessons require the modification of current processes for obtaining public input and participation in public policy decisionmaking, then the affected Federal agencies are encouraged to make such adjustments. Wherever legislative initiatives are required to foster this improved communication and coordination, the Federal agencies should make known the need for such changes.

F. INTERNATIONAL CONSIDERATIONS

In all deliberations regarding recombinant DNA research, the nature of its conduct and possible regulations thereof, American authorities must bear in mind that research in this area is going forward rapidly in other countries. During his appearance at the hearings, Dr. Donald Fredrickson, Director of the National Institutes of Health, emphasized that there is a need for substantial international cooperation in the development of any standards and guidelines which are to be applied to all areas of DNA recombinant molecule research.

The Subcommittee agrees that the United States must communicate extensively with other Nations on these subjects. The United States should also be conscious of the fact that other Nations may look at our actions in this area as setting an example for their own. Nevertheless we cannot expect other countries to copy whatever institutional mechanism is finally adopted by the United States to regulate this research: each country must choose that institutional mechanism which is most appropriate for itself.

The international considerations which concern the Subcommittee involve not only the common issues of safety discussed earlier, but also issues relating to the United States position in world science. It has been noted that Federal preemption of State and local laws governing the conduct of recombinant DNA research is one of the most important and controversial issues in the recombinant DNA debate. However, the larger issue of which this is a part involves the effects of differing regulations across national boundaries.

Dr. John G. Adams, representing the Pharmaceutical Manufacturers Association, responded as follows to the question of how more stringent State or local regulations on recombinant DNA research might affect his industry:

> . . . if a local community posed a ban or severe restrictions, standards higher than those which ultimately would be promulgated in guidelines, I think in order to continue the research and continue to endeavor they might consider a relocation of their research facility.

Particularly since recombinant DNA research appears to have considerable potential for utility in many fields and hence may result in new technologies with marked economic impact, the Subcommittee is concerned that this relocation may take place on an international level.

This concern is not merely with industrial relocation, but also with the U.S. balance of trade generally. Further, it is a situation which raises concern beyond industrial research to academic research. Any significant U.S. lag in genetic technology, for whatever reasons it may occur, could result in diminished power and prestige for this nation on the international scene. Such a possibility must not be overlooked as considerations for dealing with the recombinant DNA research issue go forward.

POST HEARING DEVELOPMENTS

Since the end of this series of hearings a number of significant events have occurred which the Members of Congress may wish to consider. A selection of the most pertinent events are sumarized in this report with references to further discussions if more details are desired.

A. Changes in Perception of Risk

Some of the scientists who first called attention to the potential for risk in recombinant research have now changed their position. These changes in perception of risk have occurred for a number of reasons. First, there has been a period of about four years of additional research; second, other scientific disciplines have contributed knowledge from the fields of epidemiology and infectious disease; a major workshop was held to examine the history of pathogenic diseases; experience has been added from international research; and work, both published and unpublished, has been completed in the laboratories of investigators in attempts to resolve some of their own ideas. It has been very difficult for these scientists to gain the same degree of acceptance of their new perceptions as contrasted with their success in gaining public awareness when they discussed the potential for risk. A major problem has been a delay in gaining the usual peer review of these new experimental data, the absence of widespread dissemination of these new opinions for evaluation by public interest groups, and, perhaps, a natural difficulty in alleviating anxieties once aroused in the mind of the public (see Washington Post, December 17, 1977, for Dr. James Watson's comments on lifting the restrictions on recombinant DNA research, Appendix).

B. Revisions of the Guidelines

The National Institutes of Health has proceeded to hold public hearings on proposed revisions of the Guidelines for Recombinant DNA Research. Although quite complicated, a number of proposals within these revisions reflect some of the thinking about the changing perceptions of risk.

Some of these proposed changes would: establish a list of experiments which would not be included in the guidelines if it could be determined that such experiments duplicate naturally occurring genetic events (this would eliminate approximately one-third of the current experiments now controlled by the guidelines); and permit the Director of the National Institutes of Health to grant exemptions for prohibited experiments. Interesting comments on the proposed guidelines included the observation that Western European nations have much less concern about recombinant DNA research than is represented in the guidelines of the United States; there is significant criticism present

with regard to the classification of the viral agents used in recombinant DNA research (viruses in general are "lumped together" rather than being classed as are bacteria in categories ranging from harmless to very dangerous); more work needs to be done in evaluating the methods of conducting certain types of research with plants; and there is still concern that the legal processes for implementing the guidelines are inadequately described within the guidelines.

A final decision on revision of the guidelines had not been made at the time of submittal of this report.

C. International Activities

A "Report of the Federal Interagency Committee on Recombinant DNA Research: International Activities" was submitted to the Secretary of HEW in November 1977. This report summarizes the status of international activities and suggests a series of actions which should be taken to insure continuing coordination of efforts to regulate this research. Copies of the report are available from the NIH Office of Recombinant DNA Activities.

D. Procedural Violations of the NIH Guidelines

Two events have occurred which support the criticisms which have been leveled at the ability of the scientific community to regulate itself as well as the ability of the NIH to regulate laboratories conducting such research. At the Department of Biochemistry and Biophysics, University of California, San Francisco, investigators completed research which led to the successful isolation of the gene coding for rat insulin in a recombinant DNA experiment. This team used a plasmid vector for the experiment which, while it had been tentatively approved by the Recombinant DNA Program Advisory Committee to the Director of NIH, had not been certified for use by the Director. The investigators apparently chose not to make public this incorrect application but instead destroyed the vector and experiments and then later repeated the experiment with approved procedures. The violation, whether technical because of ambiguous wording in the guidelines or for other reasons, created no health problem. It was not clear, however, that NIH had been fully aware of the violation until it was made public in an article in Science (Wade, Nicholas. Recombinant DNA: NIH Rules Broken in Insulin Gene Project, v. 197, September 30, 1977, Appendix). In another incident, queries by the Environmental Defense Fund led to an investigation by an NIH team which revealed that an investigator at Harvard University Medical School was conducting recombinant DNA experiments without the necessary memorandum of understanding and agreement having been filed with NIH (see New York Times, December 16, 1977 Appendix). Again, this event illustrates some difficulty that NIH has had in enforcing compliance with the guidelines and identifies at least two instances where scientists were conducting experiments with Federal funds but not in conformance with the NIH procedures. In the latter case, the investigator was denied any further use of his grant to conduct any recombinant DNA research pending the completion of an investigation into the incident.

E. Commercial Developments

In a statement in October 1977, a Federal patent appeals court ruled that an industry can patent and own certain forms of life that it develops (see Wall Street Journal, January 26, 1978, Appendix). This ruling is significant since a development by Upjohn Company opens the way for a broad spectrum of manufacturers to work with new microorganisms and could affect the work of other scientists using the DNA recombinant research technique. Associated with this ruling is the first commercial application of a development from the DNA recombinant technique. Genentech, Inc., a firm in San Francisco, has applied for the patent rights to produce a human brain hormone called somatostatin. This patent would involve the use of certain techniques employed in DNA recombinant molecule research (see Business Week, December 12, 1977, Appendix).

F. Environmental Impact Statement on NIH Guidelines For Research Involving Recombinant DNA Molecules

The National Institutes of Health published the final Environmental Impact Statement on recombinant DNA research in October 1977. The draft statement had been the subject of much controversy including citation as a factor in litigation. The final document is now available from the NIH Office of Recombinant DNA Activities.

REPORT OF THE HEARINGS*

I. The Biology of DNA Recombinant Molecule Research

A. INTRODUCTION

About five years ago, investigators in the field of cell biology discovered and made available for laboratory research a series of enzymes which permit the researcher to cut with precision the molecule containing the hereditary units which control the reproduction and functioning of a cell. This molecule, known as deoxyribonucleic acid or DNA, long a subject of intense study, now is chemically accessible for detailed examination. The enzymes permit the investigator to cut the molecule at precise locations, and to insert into the molecule new bits of DNA from any other organism. These newly formed DNA molecules, called recombinant DNA molecules, can then be reinserted into a host cell and will multiply as the host cell (or cloning cell) divides in its normal reproductive processes. The most frequently used cloning cell has been a special variant of a bacterium common in the human intestine known as *Escherichid coli* although other host cells are available. This ability to transfer, with precision, small units of DNA from one species to another, is one of the most exciting scientific developments in this century, for it offers the potential for identifying many aspects of the DNA regulatory mechanisms for which knowledge was not readily available by more traditional techniques in biochemistry and genetics.

Origin of the Technique

Chairman Thornton pointed out in his opening statement that the work which established the basic molecular structure of the hereditary units of the cell opened the door to this vast new field of research. The molecular definition of the basic structure of DNA in 1953 led to the accelerating accumulation of knowledge, including the appearance of the DNA recombinant molecule research technique, which in turn is leading toward the capability to manipulate the very fundamental biological controls of life. These new developments have produced an unexpected and almost unparalleled public interest in biomedical research. This interest has been expressed both in support of and opposition to the continuation of this line of investigation. This public involvement has induced an intense interest in the evaluation of science policies for basic research including not only the justifications for public funding for such research but also an examination of the long-term moral, legal, and ethical implications of basic research which offers the potential for eventual direct and precise control and possible intervention in the hereditary characteristics of man. In the first series

*For the complete record of the hearings see: U.S. Congress, House, Committee on Science and Technology. Subcommittee on Science Research and Technology, Science Policy Implication of DNA Recombinant Molecule Research. [Washington, U.S. Gov't. Print. Office]. March 29, 30, 31, April 27, 28, May 3, 4, 5, 25, 26; September 7 and 8, 1977. 1293 p. (95th Congress, 1st session. House) [No. 26].

of hearings on the science policy implications of the DNA recombinant molecule research issue, the Subcommittee asked selected witnesses to provide background information on the biology of this technique.

B. BASIC BIOLOGY OF THE DNA RECOMBINANT MOLECULE TECHNIQUE

Dr. Singer

As pointed out by Maxine Singer, Laboratory of Biochemistry, National Cancer Institute, all cellular or cell-like structures which are propagated, or which induce propagation, such as viruses, contain the chemical information which that cell needs to carry out its various functions (unless of course it is defective). In addition to providing this information in a precise biochemical form, the cell must also possess the ability to turn on and off various segments of this information in response to appropriate stimuli, either internal or external to the information center of the cell. Within the last several decades, this information center has been subjected to intense study in an attempt to describe its structure in precise biochemical terms. This has been accomplished and the molecule is now known as deoxyribonucleic acid or DNA. A great deal is known about this molecule and the way that it is duplicated and how information flows from this structure to regulate the activities of the cell. However, there is still a great deal more that is unknown such as the operational controls or "on-off switches" and the change in control systems which produce genetic errors. It is the need to characterize the nature of genes, and to obtain more precise data about the unknown regulators and duplication processes which is producing the pressure to develop and use the best techniques available for the study of DNA. DNA recombinant molecule research has evolved as the latest and potentially best technique now available for use in the research laboratory.

The DNA recombinant molecule technique was described by Dr. Singer. She demonstrated with a simple model the processes involved in the cutting of segments from the circular DNA (or plasmid) of a bacterium. This process involves the extraction and isolation of the DNA molecules (in her example of bacterial plasmids) using a number of sophisticated laboratory techniques. The special enzymes are used to split the molecule at precise locations and then using other techniques, the molecule can be rejoined in a similarly precise fashion. If a separate fragment of DNA is cut, from a fish for example, it is possible to add this unit of fish DNA into the piece of cut bacterial DNA. When the bacterial DNA is rejoined it will be a "recombinant molecule" of bacterial DNA containing the fish DNA. When this recombinant DNA is processed back into a bacterial cell it will be reproduced in a normal fashion except that the "recombinant molecule," which is the term used to describe the modified plasmid, now will also replicate the fish segment of DNA within the bacterial cell. Thus, the scientist in the laboratory can reproduce in a few hours, because of the rapid multiplication time of bacterial cells, a large quantity of the portion of fish DNA which was added to the bacterial DNA. This portion of new DNA can then be isolated in pure form in large quantities for further study.

An essential factor of DNA recombinant work is the survival and replication of the laboratory constructed recombinant molecule when

it is reintroduced back into a cell system. For the purpose of the Federal guidelines which are now in effect to regulate, DNA recombinant molecule research is defined as:

> * * * molecules that consist of different segments of DNA which have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host's genome.

The discoveries which were crucial to the recombinant molecule technique were the identification of the very special enzymes which permit the "cutting" of the molecules and the development of techniques to collect the small recombinant molecules and reintroduce them into a living cell so that they will replicate.

C. ALTERNATIVE TECHNIQUES

In her discussion of the technique of DNA recombinant molecule research, Dr. Singer indicated that there are several alternative techniques available. These include the standard microbiological techniques which have been used in the study of bacteria for decades—studies of mutations, deliberate induction of mutations with radiation or chemicals, selection of natural antibiotic resistant forms, natural viral transfer of genetic properties, work with sexual inheritance, and similar classic studies in bacterial genetics. These types of studies have been very fruitful in the single celled bacteria but similar detailed studies have not been possible in higher organisms. In fact, it is because of the great detail available on the genetics of the single celled bacteria *E. coli* that this organism has been the principal subject of work with the DNA recombinant molecule technique.

Dr. Singer pointed out that direct synthesis of a gene also was a new possibility for certain kinds of work; however, she emphasized that the major difficulty with this technique is the enormous complexity of the work and the amount of time to complete the synthesis (the most recent work required about nine years for one gene). Although such work does require considerable time, she considers this factor as the least important impediment to synthesis as a technique. The structure of the gene must be known before the synthesis can take place and she emphasized that the DNA recombinant molecule technique is the only practical method at this time for precise definition of structure of any number of genes, and particularly the genes of higher organisms.

The alternative to direct synthesis of genes is to use an intermediate synthetic technique in which the biochemical cell messenger (messenger RNA) for the construction of a particular protein is isolated and then used as a copying template by the researcher. Dr. Singer summarized the disadvantages of this method as including the current difficulty with isolation of the pure messenger substance (the RNA) and the fact that the control switches related to DNA activity are not amenable to examination.

Dr. Lewis

Among the alternative techniques of particular interest, Charles Lewis, Staff Scientist, Agricultural Research Service, identified fusion of a single cell from each of two plants—a non-sexual hybridization—which is accomplished in the laboratory. This is another technique by

which species which are not sexually compatible can be hybridized. The technique involves isolating live cells of the species of interest, removing the cell walls enzymatically, and then either chemically or physically manipulating the cell contents so that the cell contents are fused together. Thus the genetic information of both cells is combined. The new, combined cell is then induced to grow in plant tissue culture. There are still some difficulties to be resolved such as inducing the new hybrid to grow to maturity and inducing the growth of a new cell wall around the protoplasts. This is a technique, however, which would permit species crossing techniques although the precision of the DNA recombinant molecule method is obviously not possible.

D. SIGNIFICANCE OF THE DNA RECOMBINANT MOLECULE TECHNIQUE

Dr. Singer emphasized that the DNA recombinant molecule research technique in basic research is extremely important. The technique permits the isolation and study of very small units of DNA corresponding to one bit of genetic information. Thus the detailed study of the chemical structure of the gene is now possible. Another advantage of this technique is that the researcher also can study the gene or units of the total DNA molecule which turn on and off the process of information transmittal or replication within the cell. Knowledge of the chemical nature of these switches is of extreme importance and not readily obtained by other methods at the present time.

Dr. Singer summarized the importance of the DNA recombinant molecule technique as now permitting the study of:

(1) the structure of the individual genes;
(2) the nature of the control mechanisms that switch genes on and off; and
(3) the manner in which proteins are made in a cell.

Potential for Agriculture

In support of Dr. Singer's comments about the significance of the DNA recombinant molecule research technique, Dr. Lewis indicated that agricultural scientists perceive great potential for accelerated research in plant and animal genetics. As he noted, there has been a dependence in agriculture upon improvements achieved through more traditional genetic methods. As he summarized these methods, he emphasized the gradual nature of the improvement of plant and animal varieties through early selection methods, then on to the more precise control of hybridization processes by the modern agricultural research scientists. All of the methods discussed by Dr. Lewis highlighted the dependence upon what he refers to as essentially a sexual, cellular approach. He did point out, however, that even in these genetic methods, researchers were essentially speeding up natural processes and directing the selection process toward goals defined as advantageous for the solution of agricultural problems. From this level of perception, Dr. Lewis indicated that agricultural scientists recognize that the DNA recombinant molecule research technique expands considerably the range of man's potential for manipulating life forms. Of particular interest is the increased capability to provide for the transfer of characteristics which are not normally transmitted by sexual processes between widely separate species.

Dr. Wald

George Wald, Harvard University, voiced his concern about the significance of the DNA recombinant technique. As he discussed his observations on this issue, he asked whether society really should support the development of knowledge which would provide the ability to tamper with or otherwise modify all living organisms. He regards this issue as a major question which must be addressed more adequately before any final decision is made regarding the regulation of such research. He did caution, however, that he should not be misinterpreted as wishing to deny access to knowledge. With reference to the availability of alternate techniques for acquiring basic knowledge about the structure of DNA, he suggests that many of these methods, while requiring more time, could provide similar data with less risk or interference with evolutionary barriers to gene transmittal. As Dr. Wald pointed out, he would have little difficulty in accepting the use of the DNA recombinant molecule method if the research was limited to the little or no risk category (permitted under P1 experimental conditions) and which restricted the experiments to species which regularly exchange genes in nature. His comments make obvious the concern felt by other investigators as well that this technique is significant since it represents a tremendous stride toward capabilities which have not been fully assessed.

Dr. Baltimore

David Baltimore, Professor of Microbiology, MIT, made a number of comments about the importance of the use of bacteria in the DNA recombinant method. First as noted before, bacteria contain a much smaller number of genes and can be easily manipulated in the laboratory. They have been easier to study genetically than higher organisms. This simplicity is relative to the more complex DNA in higher organisms for even with the bacteria progress has been slow. Recombinant DNA technology has offered a partial solution by permitting the study of the genes of higher organisms by placing them in the simpler genetic environment of bacteria. Individual mammalian or other genes can be isolated and their function studied independently.

II. THE OBJECTIVES AND STATUS OF THE DNA RECOMBINANT MOLECULE GUIDELINES

A. Introduction

At the beginning of the controversy over the use of the DNA recombinant molecule technique, the primary issue was one of the potential for possible hazard to the public health and safety. With this issue as a focus of attention, the scientific community identified a series of requirements for conducting approved research, which they believed to be suitable for assuring the continuation of research with a minimum of potential for harm. Basically, these requirements are divided into two forms of containment: physical barriers utilizing the best technologies for safe handling such as hoods for safeguarding the dissemination of aerosols, high temperature autoclaves for disinfecting, filters, negative pressure and similar laboratory architectural and equipment requirements; and the use of a unique biological method of deliberately selecting for experimental use mutant organisms which lack the capability to survive in nature because of unique growth requirements available only in the laboratory medium in which they are grown. These requirements have now been promulgated by the National Institutes of Health as guidelines to be followed for all DNA recombinant molecule research supported by Federal funds.

B. Physical Containment

Dr. Barkley

Emmett Barkley, Director, Office of Research Safety, National Cancer Institute addressed the development and utilization of physical containment standards which are being prescribed for all federally funded DNA recombinant molecule research. As he pointed out in his introductory comments, the objective of physical containment standards is to confine to the laboratory the research organisms containing recombinant molecules. Four levels of physical containment are specified within the DNA recombinant molecule Federal guidelines. These levels are code designated P1, P2, P3 and P4. The least potentially hazardous experiments are permitted under P1 conditions and the experiments about which there is the least information and which are estimated to have the potential for a relatively high degree of hazard are assigned to the P4 type of laboratory.

The P1 level of containment is fundamentally the use of good microbiological practices. P2 provides for a combination of good microbiological practice plus the use of certain types of containment equipment and the specification of good sanitation procedures. At the P3 level more stringent microbiological laboratory practices are specified, entry and exit procedures are imposed to minimize transport out of the laboratory of possible contaminating substances, and facility safeguards such as double-doored entrances, controlled

airflow, control of exhaust air and similar protective measures are mandated. Physical containment providing the highest possible safeguard is provided within the P4 facility. This type of facility builds on the preceding criteria and adds additionally stringent measures such as the use of special handling cabinets (under negative air pressure), filtering of all air through high-efficiency particulate air filters or filtering and incineration of air, careful sterilization procedures, the use of chemical decontamination tanks, and a series of secondary safeguards such as air locks, clothing change and shower rooms, biowaste treatment facilities, and separate ventilation systems.

Secondary Safeguards

As pointed out by Dr. Barkley, the use of secondary safeguards is primarily an added safety factor not generally used in the typical microbiology laboratory even where pathogens are handled. However, in the opinion of the advisory groups which established the requirements for DNA research, the additional use of secondary facility safeguards for experiments confined to P3 or P4 facilities will make any possible or potential hazard to the public from such research even more remote.

Dr. Barkley then provided a summary of the history of accidental infections which had occurred in laboratories which had been handling extremely dangerous pathogens, such as in the research at Ft. Detrick on biological warfare agents. According to his testimony, while accidents had occurred, the frequency of these accidents was quite low and there had never been any epidemic episode outside the laboratory and within the surrounding community. This knowledge, based upon experimental work under conditions less stringent than proposed at the P4 level, provides the designers of the physical facilities with a high degree of assurance that compliance with these requirements provides an extremely high degree of safety. Dr. Barkley indicated that he was aware of 25 government, 4 university, and 5 industrial facilities which currently provide most of the primary and secondary safeguard requirements for a P4 facility (although these facilities are not yet certified as P4 facilities). All of these facilities would require additional work to be fully certified for P4 research.

Dr. Barkley expressed his professional opinion that the combination of the prescribed physical containment facilities with an appropriate attitude, diligence, training, and proficiency on the part of the laboratory workers would provide the capability to protect the public from any potential risks postulated for this work. As also pointed out by Chairman Thornton, however, the fact that accidents had occurred was an indication that the decision to incorporate the safety precautions provided by the addition of biological containment requirements was wise.

C. Biological Containment

Dr. Curtiss

Biological containment, as described by Roy Curtiss III, Department of Microbiology, University of Alabama Medical Center, involves the use of viral and plasmid cloning vectors (constructed into recombinant molecules as described by Dr. Singer) which have been

genetically altered by traditional microbiological genetic procedures to produce a dependence upon certain growth conditions and upon a particular host cell strain, also "crippled" to be dependent upon precise growth conditions. This combination of a sensitive vector for constructing the DNA recombinant molecule and a host cell for the cloning of the new DNA recombinant molecule is considered to be a significant part of the system which has evolved to permit the conduct of DNA recombinant molecule research under extremely safe conditions. As pointed out by Dr. Curtiss, the use of the K–12 strain of the bacterium *Escherichia coli* was due to the tremendous amount of information available on the genetics of this bacterium and the long laboratory experience in work including the initial DNA recombinant molecule research. It was thus only natural to continue to work with the K–12 strain during the development of biological containment systems. By using the lowest level of detectability possible with current techniques as the measure of permissable survival of a potential vector or cloning cell, the microbiologists worked toward the selection of vectors and host cells which would prevent any inadvertent survival or transmission of DNA recombinant molecules outside the research environment. The investigators engaged in the "construction" of such "weakened" variants then must provide data which demonstrates that the proposed vector and/or cloning cell meet the criteria for use of a particular kind of research. Dr. Curtiss expressed his opinion that when the proper combination of biological containment and physical containment are utilized, there should be essentially no hazard under the types of experiments permitted by the guidelines. He did caution, however, that the human factor is always involved in such experiments; thus there is a continuing need to insure appropriate training of individuals engaged in such research in order to minimize any potential error.

D. The NIH Guidelines for DNA Recombinant Molecule Research

Dr. Fredrickson

Donald Fredrickson's (Director of the National Institutes of Health, DHEW) testimony was primarily a summary of the current status of the NIH DNA Recombinant Research Guidelines. As Dr. Fredrickson pointed out, compliance with the guidelines is now a requirement for all research funded by NIH. Because of the efforts of a special Federal Interagency Committee on DNA Recombinant Research, the Director indicated that all other Federal agencies who might fund similar research would also require compliance with the guidelines. Dr. Fredrickson noted that he was very aware of the need for careful public as well as scientific consideration of the Federal actions with regard to regulating this type of research and summarized a number of steps which had been taken by his office to provide for public involvement in the development of the guidelines as well as other actions being taken at NIH.

The NIH has established a Recombinant DNA Molecule Program Advisory Committee which reviews the guidelines and provides recommendations to the Director for needed changes. This Advisory Committee also serves to review proposals for the approval of vectors

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or cloning systems to be used in the DNA recombinant molecule research and provides recommendations to the Director for adoption or rejection of such systems. The Advisory Committee to the Director of NIH has had the task of assisting the Director in reviewing the recommendations of the DNA advisory committee and comments from the public. Both of these advisory committees have membership not only from the scientific community but also from other disciplines such as law, ethics and consumer affairs. Copies of the guidelines and of the proceedings of the meetings of these advisory committees are widely disseminated to the public and are available upon request. Further, the NIH has established a new Office of Recombinant DNA Activities to administer and coordinate intramural and extramural activities at NIH; to review the institutional biohazards committees which are required by the guidelines; and to monitor reports and information concerning accidents, containment and safety research innovation. The other area of importance has been the drafting of a proposed Environmental Impact Statement on DNA recombinant research.

Extension of Guidelines

A separate task of the Federal Interagency Committee on Recombinant DNA Research, created with the approval of President Ford, was to examine the need to extend the NIH guidelines to the public sector or private sectors not funded by Federal funds. This committee reviewed the actions being taken by other nations of the world to control or regulate DNA research. As Dr. Fredrickson noted, several countries have already established their own guidelines to govern such research. The Director indicated that he had personally visited several of the Western European Nations to discuss this issue. It appeared at the time of his testimony that the regulatory work in other nations is being carried out almost entirely by advisory committees, some of them quasi-governmental, others private in nature. The debate on this issue in these other nations has not been as widespread or time consuming as it has been in the United States. There seems to be general agreement that the standards for regulating DNA recombinant research should be uniform on an international basis. With the evolution of uniform guidelines, a major task now seems to be to try and develop a more or less uniform method of insuring that the guidelines are enforced.

In reporting further on the work of the Federal Interagency Committee on DNA Recombinant Research, the Director indicated that this body also had examined the applicability of existing legislation to provide regulatory authority. The committee's conclusion was that no single legal authority or combination of authorities now exists that clearly permits regulation of all research or other uses of recombinant DNA techniques. Among the conclusions reached by the committee in terms of needed authority, agreement was reached that: (1) registration of projects involving the use or production of recombinant DNA molecules is needed; (2) facilities should be licensed including an acceptance by the facility of responsibility for the activities at the facility; (3) a single set of national standards should govern and local law should be preempted to insure national standards and regulations; (4) DHEW should continue to cooperate and coordinate with relevant Federal departments or agencies in this matter.

New Ethical Factors

Dr. Fredrickson indicated his belief that biomedical research is entering a new era in its relations with society. The DNA recombinant molecule research issue has highlighted the public concern in this new era. In his view, biomedical research is moving from an area of privacy and autonomy to new ethical, legal and social imperatives involving a need for scrutiny. The response of NIH has been to form review boards to oversee experimentation with human subjects, promulgation of animal care regulations, and the new emphasis of public involvement in the DNA recombinant molecule issue. He conjectured that similar bodies may soon have to oversee other hazardous laboratory research. Dr. Fredrickson believes that this new involvement of the public in science policy determination is an adjustment to the need for insuring the public that such research is being conducted safely and for the public good, but also that care must be taken to insure that successful research is not impeded or creativity hampered.

Dr. Fredrickson stated that he does not believe that we could make a really useful technology assessment on DNA recombinant research at this time beyond imagining various scenarios for examination. There is not enough evidence now to adequately assess this new technology.

Control of Research

With regard to the guidelines, both Dr. Wald and Dr. Curtiss indicated considerable concern about factors related to but not a specific part of the proposals to extend the guidelines to all DNA recombinant research. Dr. Wald summarized his view that a general application of the guidelines to all DNA recombinant research is being viewed by some scientists as a foot in the door to regulation and control of all biological research. His discussion suggested a fear on the part of some scientists that an expanded regulation of such research would have a harmful effect on the spirit of free inquiry. [He suggested applying the guidelines only to the P2–P4 cateogories of risky research and limiting this research to a few national laboratories in order to avoid excessive regulation of all laboratories.] Dr. Curtiss suggested that the guidelines may actually be "overkill" in their protective specifications and that the recognition of an "excessive" conservatism by scientists might cause the guidelines to be treated in a cavalier fashion in much the same way that other sorts of laws which are unnecessary or unrealistic are frequently disobeyed by individuals who view the law in this fashion. He seemed concerned that overly restrictive regulation might produce contempt and a refusal of cooperation.

Dr. Nathans

During his discussions of the potential risks which might be hypothesized for DNA recombinant research, Daniel Nathans, Johns Hopkins University School of Medicine, emphasized his opinion that the NIH guidelines are conservative. However, he supports this conservative approach until such time as evidence is accumulated to further reduce any of the uncertainties causing concern about safety.

Dr. Baltimore

Dr. Baltimore indicated that he would prefer to see Federal regulation of DNA recombinant research in a uniform fashion rather than

an evolution of patchwork regulation within governing jurisdictions of varying size (that is, city, county, State, etc.) which in his opinion would be an intolerable situation for the scientific community. (This assumes that each jurisdiction would develop nuances of differences in their own approach to regulation.) If it is true that no existing Federal laws will permit regulation of this area of laboratory research then he feels that the Congress should construct such legislation at the Federal level, once it determines that legislation is needed.

E. Industry Views

The guidelines are only enforceable as regulations at the present time on federally funded research. Although there has been a general indication that private firms would follow the guidelines voluntarily, there has been public concern about how such compliance would be assured. Further, some of the discussions regarding industry compliance have led to accusations that manufacturers could not be expected to follow the guidelines because of problems in dealing with trade secrets, patents, and limitations on quantities of materials permitted under the guidelines. John G. Adams, Vice President for Scientific and Professional Relations and Bruce J. Brennen, Vice President and General Counsel for the Pharmaceutical Manufacturers Association (PMA) provided their comments to the subcommittee.

Dr. Adams

In his testimony, Dr. Adams indicated that three PMA firms were directly engaged in DNA recombinant molecule research and three other member firms were supporting academic research. All are committed to voluntary compliance with the NIH guidelines. Dr. Adams also indicated that PMA had participated in discussions with NIH during and following the publication of the guidelines, as well as in discussions with the Department of Commerce. In all testimony before both House and Senate committees, the position of the PMA has remained unchanged. Although the member organizations are committed to voluntary compliance with the NIH guidelines, the guidelines were written exclusively for research organizations, therefore there are some adjustments which will be required in the operative portion of the guidelines in order for the technology to be used commercially. Their concerns relate primarily to administrative features and not to a desire to reduce either the biological or physical containment features of the guidelines. Points of particular concern include the need for protecting the confidentiality of information submitted to the Government in compliance with requirements for inspection and reporting and a concern about the limitations on the volume of cultures prescribed in the guidelines. Commercial practices would necessitate the use of larger volumes for scaleup of any process of commerical importance.

Federal Prescription

According to Dr. Adams, the Association advocates Federal legislation and supports licensing and inspection of facilities, registration of research projects, and mandatory submission of reports. Member firms also endorse the promulgation of regulations based on the existing NIH guidelines to make them applicable to all persons engaged in

recombinant DNA research. Since the use of institutional review boards or institutional biohazard committees are routine in their research they also support this requirement. They endorse Federal preemption of State and local laws in order to insure uniformity of standards. They oppose specific restrictions on patent laws proposed in some legislation including any provision which would use patent restriction as a lever to insure compliance with the guidelines. There are other administrative provisions of proposed legislation which require modification in the view of the association but these should be easily remedied once all of the alternative provisions are placed in proper legal perspective.

Dr. Johnson

In further examination of industry views on this issue, testimony was obtained from Irving S. Johnson, Vice President, Eli Lilly Co. In general, Dr. Johnson's statements endorse the views presented by Dr. Adams of PMA. As he pointed out, his company is engaged in research to evaluate potential applications for recombinant DNA technology. They are attempting to use the technique with antibiotic-producing organisms and are evaluating the possibility of producing medically useful hormones and other proteins. Dr. Johnson indicated that his firm has provided for public participation in many of the meetings held with regard to the guidelines including participation in the National Academy of Sciences' public forum on this subject. The firm has made a special effort to provide information on its research in this area to the news media, via radio, television, newspapers and journals, and to its stockholders. Lilly also convened an international symposium to discuss the possibility of utilizing recombinant DNA techniques in insulin biosynthesis. He emphasized that the company has not made any secret of its interest in this area of research.

Dr. Cape

In his observations on industry reaction to the proposed regulation on DNA recombinant molecule research, Ronald E. Cape, President, Cetus Corporation, indicated that at the present time there is no general focal point for obtaining industry reactions—a desirable state of affairs from his own personal perspective. Each of the various industries proposing any potential applications will have a different view regarding its estimates of needs and problems needing resolution for commercial application. From his own perspective as a representative of his company, Dr. Cape indicated that public inquiry into the issue was welcome. He noted that science is for the people, and although the heavy involvement of public funds has resulted in a natural desire for some return on this investment by the public, the organization of our society places the task of commercialization on industry. He emphasized that his company would under no circumstances undertake any research in this area without complying with the guidelines even though there was no legal obligation to do so. He indicated that some sort of legislation requiring legal compliance with regulatory requirements in a uniform manner is probably desirable and inevitable. His reaction was that since commercial application of any research successes will be slow, so also should the development of the final form of any legislation be careful and thorough. His explanation for some of the reports

suggesting a reluctance of industry to fully comply with the Federal guidelines was that it is not possible to commit resources to a course of action until it is known to a higher degree of precision than is now possible just what the course of action will be. In other words, while the industries view compliance with the guidelines as a necessary part of business, additional funding to provide facilities will be necessary when and if such development occurs commercially. Industries want to know more about the precise requirements with which they will be confronted before they indicate more formally their willingness to follow such guidelines or to commit resources to meet such regulations.

Long-Term Interests

The industrial view will be more long-term than the basic researchers' perspective according to Dr. Cape. Commercial application of DNA recombinant techniques will require extreme safety because applications years in advance cannot be assumed and funds provided unless there is a high degree of assurance that untoward effects will not occur and block utilization of such processes. For this reason, industry will be examining a number of alternative organisms and research systems, and hopes to find even safer systems than *E. coli* if this is at all possible or necessary. In order to meet economic demands, considerable developmental work will be required. None of this will happen quickly, and so there should be time for careful, considerate development of the best way to meet any potential hazard issues while at the same time not adding unnecessarily to the costs of rate of development. Disincentives to development could occur and deny opportunities for commercialization should excessive regulatory requirements evolve. Since any commercial exploitation is still long-range in potential application, all of the problems and programs cannot be identified with precision; however, experience with other commercial developments of this type indicate the stages from the research to profits are long and fraught with difficulty and many failures.

On the other hand, Dr. Cape indicated that less dramatic developments may evolve more quickly from DNA recombinant research which will improve current processes such as better microorganisms for industrial fermentation—cheeses, antibiotics, beer, etc. He considers this an important possibility today because it may enable us to move from decreasing supplies of petroleum as a source for many industrial chemicals to other renewable resources. More than likely, the first commercial applications will be in these less glamorous and less dramatic areas of improved efficiency of existing processes.

III. THE PLACE OF RISK/BENEFIT ANALYSIS IN SCIENTIFIC RESEARCH—DNA RECOMBINANT RESEARCH AS A CASE HISTORY

A. Introduction

Chairman Thornton pointed out that the testimony of the various witnesses frequently made reference to the problem of evaluating the risks and benefits of DNA recombinant molecule research. In fact, it was obvious during much of the testimony that risk/benefit analysis has become an increasingly important factor in judging many issues in science policy, science and technology. However, the value of risk/benefit analysis becomes more and more tenuous as the estimates include highly speculative data. An important question addressed during these hearings was: What are the utility and limitations of risk/benefit analysis techniques in decisions involving science and technology? Since a focus of attention during the hearings was the DNA recombinant molecule research issue, the risks and benefits perceived for this area of research received primary emphasis. However, the broader scope of decision-making in science policy also was addressed by several of the witnesses in an attempt to highlight some of the major principles of risk/benefit analysis.

B. Risk/Benefit Debates in DNA Recombinant Molecule Research

As noted on several occasions during the hearings, one of the benefits of the DNA recombinant technology is that the function and organization of genes can be studied as they relate to an understanding of disease. The use of this technique could speed the acquisition of this knowledge. Until this knowledge is available, it will be impossible to predict how or in what specific applications such knowledge will be important. It was emphasized that DNA recombinant technology is a tool of research and in itself offers no benefits. It is the information which can be extracted by using this tool that offers a potential for benefiting mankind. Like the benefits of other basic research in biology, it is impossible to predict with a high degree of precision just what these benefits will be. As an example, Dr. Baltimore pointed out that one of the leading investigators in basic research of the causes of cancer believes that much more work is necessary. DNA recombinant molecule research is an important tool for this work. Those who believe that prevention is more important than cure of this disease must recognize that before prevention is possible, cause must be determined. Other witnesses pointed to the high incidence of genetic disease and the need to acquire knowledge about these diseases. It may even be possible eventually to provide a permanent correction for such harmful defects.

Dr. Cape

Dr. Cape indicated that the beneficial outcome of DNA recombinant research will probably fall into two categories: (1) fundamental understanding of the processes of life generally and (2) facilitation of the development of products and processes not now possible—such as vaccine developments, synthesis of new biological products, etc. [The recent successes in the cloning of the gene for rat insulin and the use of DNA recombinant techniques to make the first functional protein, the hormone somatostatin, tend to support Dr. Cape's observations about the immediate practical value of the technique.]

Dr. Lewis

Dr. Lewis indicated in his testimony that most of the potential benefits from recombinant DNA research methods are highly speculative; as are the many risks hypothesized. He did suggest several areas where important advantages might be obtained. He cited the desirability of increasing the nitrogen fixing capability of important agricultural crops in order to decrease dependence upon artificial synthesis of nitrogen containing fertilizers. He also suggested the possibility of constructing biological controls for important insect pests which might provide a high degree of specificity of control with no danger to the environment. Other areas perceived as important fields of investigation would involve modification to improve the efficiency of photosynthesis, the construction of hybrid organisms to improve the efficiency of the digestive processes in ruminant animals, and acceleration of the acquisition of the basic knowledge about life processes generally. In fact, as noted by Dr. Wald, in his opinion the only sure benefits from DNA recombinant molecule research are going to be clarification of basic biological problems.

Dr. Baltimore

Two basic risks in DNA recombinant molecule research were identified by Dr. Baltimore. One of these is the ever present possibility that deliberate misuse of the knowledge of DNA recombinant research might lead to harm, while the other is the social misuse of the technique. In the first category biological warfare is an issue, in the other, genetic engineering of human beings might be a possibility. The International Biological Weapons Convention prohibits research for developing biological warfare agents and the DNA recombinant technique is included in the scope of the convention. In the case of genetic engineering, the nearest immediate application in human beings is the replacement of defective or missing genes which cause disease. One strategy for social control of this research would be to prohibit its refinement. However, the possibility of being able to treat genetic diseases more effectively would thereby be denied. The potential for producing changes in hereditary characteristics which would be a permanent change in species is only conjectural at this time.

The deliberate or accidental misuse of the technique might produce harm in the form of some unexpected infectious disease organism. This risk might occur should some harmful organism be constructed during experimentation. Dr. Baltimore indicated that he is much less concerned about this type of risk today than he was when the issue

was first addressed during the call for a moratorium on certain kinds of experiments several years ago. It is his opinion at the moment that the risks which are being discussed in the popular press are widely overstated. The NIH guidelines as they have evolved provide for either a total ban on undesirable experiments or biological and physical containment provisions which appear to be entirely adequate to cope with this latter type of risk.

Dr. Signer

Ethan Signer, Professor of Biology, MIT, was quite positive in his view that there is no need to accept any risk for DNA recombinant research simply on the basis of benefits which have been hypothesized. For each benefit which has been identified, he pointed out that alternative methods could be utilized to obtain the information. For example, he suggests that improvements in current methods for isolating insulin from biological materials could prove to be more effective and safer than a method involving culturing through DNA recombinant molecule methods. An attempt to resolve the world food problem by improvements in photosynthetic efficiency or through expansion of the nitrogen fixing capability in plants is an attempt to solve the wrong problems. According to Dr. Signer, the world food problem is a distribution problem exacerbated by political decisions. Reductions in requirements for nitrogen fertilizers will do little to alleviate these social maladjustments. Technological solutions, in other words, particularly with sophisticated techniques like DNA recombinant research, are not the practical solutions needed at this time. He views the DNA recombinant molecule research method as just another tool and one which should be outlawed on an international basis. He does not think that any method for controlling the use of the technique can ever be effective. Since it is relatively simple to conduct research by this technique, he expressed the opinion that effective control of containment or methods will be impossible and that, after an initial flush of concern, researchers will gradually develop a contempt for the guidelines. The longer the work continues without an accident the more any initial concern will be reduced. High containment research will be moved to lower containment requirements as risk perceptions are reduced. From this position, he feels that eventually there will be an accident which will result in the release into the environment of some recombinant DNA molecule which will have unexpected and unpredictable adverse effects on a widespread scale. Since we know next to nothing about ecological imbalances, there is no way to measure the potential for such risks.

Further, he stated that DNA recombinant molecule research will move us closer to the probability that actual genetic engineering of human beings will be possible. And if such a possibility occurs, then it is his opinion that the technology will be used. For this reason, he believes that the research should not be permitted to continue.

Dr. Nathans

In his analysis of the potential risk for either producing new pathogenic strains of micro-organisms or for seriously disturbing natural evolutionary processes, Daniel Nathans, stated that it appeared to him

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that there is no reason that research with recombinant DNA should be particularly hazardous. In support of his observations, he highlighted the fact that the Earth is populated with highly specialized and competitive organisms. Only a tiny fraction of these microorganisms produce disease. Experience has shown that even these pathogens tend to lose their disease-producing capacity when grown in the laboratory. In other words, virulent organisms become nonvirulent when cultured in the laboratory medium. If the concern is that a harmless organism, such as the variant of *E. coli* used in recombinant molecule research may be converted into a pathogen, then one would have to assume that there is a reasonable certainty that some unexpected event would provide characteristics to the organism which would enable it to compete successfully. He pointed to historical evidence which indicated that the *E. coli* K-12 variant had lost its ability to colonize the human gut except under very unusual conditions. He also suggested that the available evidence of a pathogen's success in causing a disease shows a dependence upon so many special conditions that it would probably even be difficult to deliberately construct a pathogen from the *E. coli* K–12 variant.

Although there are other hazards to be considered, such as the transfer of genes from a harmless *E. coli* variant to some other microorganism, it was Dr. Nathans' opinion that even here the available evidence suggests that such recombinant molecules would not survive outside of the laboratory environment.

Dr. Nathans also responded to the charge of a potential risk of breaching so-called "genetic barriers" against interchange between species. He cited the opportunities for potential migration of DNA units from species to species already existing in nature, and suggested that if such interchanges could occur they probably have been tested naturally under a variety of circumstances. Examples of opportunities for interchange of genetic material in nature include the existence of pathogens in the human body in direct contact with human cell contents, viral exchanges between cells of many species, the exposure or intimate contact of microorganisms to the contents of cells of enormous variety during the process of decay and decomposition, and the effects of long-term evolutionary selection pressures. Although there is no way of being absolutely certain that natural recombinant molecules are being formed, there is evidence which suggests that such events do occur and that a more careful search would probably enable these to be identified. This would suggest in turn that the use of the DNA recombinant molecule technique by man may not be unique in itself, although the establishment of laboratory conditions insuring the survival of large numbers of organisms containing such recombinant molecules is not strictly analogous to natural processes.

Conservative Approach

Dr. Nathan's general conclusions lead him to believe that the NIH guidelines provide a high degree of conservatism and that although the possibility of some potentially harmful recombinant being produced cannot be definitely excluded, the probability of such an event is very unlikely. He supports the conservatism of the guidelines until such time as more evidence is accumulated to support a view that further reduces some of the uncertainties about the available evidence on safety.

In discussing the idea that DNA recombinant research has the potential for creation of some new monstrous organism because species barriers can be crossed, Dr. Lewis indicated that agricultural researchers have learned from more traditional work that plants and animals whose systems have been modified by extreme genetic modifications usually do not survive—there are spontaneous abortions, sterility, and ecological weaknesses; highly adaptive organisms are not readily achieved by such discordant changes. However, as may be inferred from comments by critics the natural "protective" mechanisms of removal of extremely modified organisms produced by traditional methods in genetics may not function following applications of the DNA recombinant technique: this technique is more subtle. Researchers are as yet unable to be absolutely certain that the inserted DNA and its interaction with the total DNA is so well characterized that highly adaptive and undesirable life forms will not be produced and survive as a result of *less* discordant changes. In fact, one of the reasons for inserting a particular piece of DNA is to find out its role and function and the manner in which it is regulated.

Dr. Pieczenik

Among the several topics of interest in this scenario is the potential interference with "natural" evolutionary processes and the competition of one piece of DNA and its position relationship as contrasted with the "natural" sequences of DNA which have survived within an organism. George Pieczenik, Rutgers State University, discussed his research on the survival of DNA units within the total milieu of the cell. After associating the events hypothesized with the evolution of a particular combination of genes within an organism, Dr. Pieczenik indicated that he believed that the chance of an extreme taxonomic cross of DNA expressing its information would be very unlikely. He supported his observation by reviewing the number of events which would have to be favorable in order for an artifically constructed genome (gene series) to be successfully established in competition with other series. He has examined this issue and arrived at his conclusions on the basis of a theory that DNA survival within a cell is analogous to survival of an organism within an environment. That is, competition for substrates within the cell determines whether a particular sequence confers a survival advantage for a cell in competition with other DNA sequences.

He also expressed the opinion, however, that vestigial or even random expressions of DNA functions are much more likely to occur considering the present level of research competence. Thus he perceives events which are unexpected to be more of a problem than the changes which are deliberately being attempted. Accordingly, he does not see any immediate hazard or benefit from artificial DNA selection—that is, laboratory initiated construction of DNA recombinant molecules. Nevertheless, he does believe that there are certain steps which should be taken with regard to the regulation of DNA research. These include: (1) the oversight of the research should be conducted by scientists not directly involved in the work; (2) any regulating board should provide for membership from informed lay public, journalists, political representatives, union representatives, and scientists not involved in the directly related fields; (3) the background of the members of any scientific advisory board should be free

of any history of supporting morally unacceptable experimentation; (4) the principal investigator of the grant should have the direct responsibility for the research. The delegation of responsibility to juniors, such as pre- or post-doctoral researchers, should not be permitted.

Associated with Dr. Pieczenik's theory of molecular competition, is the possibility that natural recombination of DNA, involving properties not specifically associated with the growth of a particular organism, might be common. This is an important factor in the DNA debate for if recombination of DNA from different species does go on to any significant extent in nature, then the concept that man's attempts in the field of DNA recombinant research are exceptional would require further evaluation. In fact, the trend in the NIH guidelines is to decrease the estimate of the risk in this research if it is known that exchange does occur naturally between or within species. As pointed out by Dr. Wald in his testimony, he felt no strong objection to experimental work within the same species which are known to exchange DNA.

Dr. Ryan

Robert J. Ryan, Department of Molecular Medicine, Mayo Medical School discussed his observation that more than one species of bacteria may bind human chorionic gonadotropin, a protein of importance in mammals but with no known usefulness in the bacteria. Although the evidence at this time is not conclusive, Dr. Ryan indicated that it was sufficient to warrant a continuation of their effort to examine the possibility that a bacterial plasmid might contain mammalian DNA. As he indicated, the availability of the DNA recombinant technique might make it possible to examine this problem in more detail than any other method. He highlighted the point that this is the way that research works. One can never tell just how or when a particular piece of research might foster developments in a totally unexpected way. It is because of the impossibility of predicting the usefulness of a particular direction of research, that it is necessary to maintain an environment of free inquiry.

Dr. Cavalieri

In his critical evaluation of the proposed benefits to be expected from recombinant research, Dr. Cavalieri pointed out that there are over 2,000 genetic disorders, each of which would require a precise type of genetic "cure." The development of such "cures" by recombinant processes would be a monumental undertaking involving a great investment in research resources. Since there are alternative medical procedures being developed for the more frequently encountered genetic diseases, it will be necessary to continue public examination of the investment in research and to establish priorities. His comments suggest that DNA recombinant research as a practical and safe method for solving problems in this area should be classified at a lesser priority than other research areas. He was particularly interested in directing attention at the immediate benefits which could accrue should a strong emphasis be placed upon preventive measures, particularly in reducing the incidence of cancer, rather than in continuing to move into new areas with the potential for treatment.

Dr. Cavalieri's concern also focused upon the perception that time is of the essence in moving on into DNA recombinant research. He suggested that a more thoughtful consideration of the long-range implications of this area of research might produce a more conservative attitude about its value. He referred to the problems which he thinks were produced by a precipitous rush into research and development in the field of the nuclear sciences. In this regard, he reemphasized his belief that there is a need for a significant change in the attitude of scientists about their social responsibilities.

Dr. Charache

Critics of the scientists who developed the guidelines have had a number of objections to the technical writing process. One criticism which has been voiced frequently is that there was a failure to include individuals with long experience with epidemiology, the study of infectious disease, or with the conduct of work within a hospital laboratory working with infectious organisms In order to gain the points of view of such individuals, the subcommittee asked Patricia Charache, Johns Hopkins University Hospital and Samuel Formal, Chief, Department of Bacterial Disease, Walter Reed Army Institute of Research to discuss the risks which they envision with regard to DNA recombinant research.

Dr. Charache is a member of a Biohazards Safety Committee which has the responsibility for the safety of DNA research at Johns Hopkins. Before commenting on the specific issue of DNA recombinant research, Dr. Charache pointed out that bacteria differ in the degree of hazard posed in working with them. Some infect directly, others produce toxic substances which may poison an individual. As she pointed out, the NIH guidelines are predicated upon a knowledge of these differences in hazard and prescribe either a prohibition of recombinant molecule research with certain types or require varying degrees of biological and physical containment. Dr. Charache mentioned as pertinent to the evaluation of risk the fact that the condition of the person at the time of exposure may determine the reaction to the infection. It is for this reason that the guidelines caution against the conduct of research with recombinant molecules by individuals who are on antibiotic therapy, for example.

Dr. Charache also pointed out that the prescription of genetic recombinant standards for experimental organisms is not new and that long ago it had been determined that semipurified DNA could pass genetic characteristics between organisms. At that same time, experimenters had learned to use genetic markers to insure safety. It was recognized that bacteria exchanged genetic information under natural conditions including the transfer of antibiotic resistance traits. At Johns Hopkins, about 20 DNA recombinant molecule research projects have been reviewed thus far. All proposals are reviewed annually or more frequently if changes are proposed. The guidelines have been implemented without difficulty and their committee considers work with *E. coli* to be a relatively nonhazardous task. They currently have six laboratories doing this type of research and have the capability to conduct investigations requiring P3 levels of confinement.

Dr. Formal

Dr. Formal discussed his knowledge of the transmissibility of *E. coli* in human beings. As he pointed out, the growth and development of this organism in various individuals will vary depending upon a number of conditions. While the causation of *E. coli* induced disease which occurs at times is not fully understood, in a few instances, the characteristics of the strains which produce some diseases are reasonably well defined. In the work being conducted, the properties of *E. coli* which are believed to be associated with the induction of disease have been deliberately added to non-virulent strains, such as the K–12 used in DNA recombinant work, in attempts to convert this strain to a virulent variant. These attempts have failed. Although their group is continuing the studies to identify and replace all of the factors needed to induce virulence in the K–12 strain, they have not been successful. According to Dr. Formal, this suggests that there are a large number of genetic factors which must function in concert in order for the K–12 strain to recover the capacity to survive outside of the laboratory environment and induce disease.

Despite this long history of work with *E. coli* variants there has never been any incidence in which an epidemic has occurred. In response to a remark that the failure to keep records might be the reason for this lack of evidence rather than an inability for the organism to infect, Dr. Formal indicated that he believed that while the spread of nonpathogenic organisms would be difficult to monitor in any event, the evidence which is available strongly suggests there should be little concern about causing a disease with the K–12 variant. However, as pointed out by both Dr. Pieczenik and Dr. Charache, care must be taken to insure that traits are not transmitted to the laboratory strain which would permit it to infect other more pathogenic strains. Such steps have been outlined in the NIH guidelines.

Dr. Curtiss

With regard to the risks of epidemics from recombinant work with *E. coli*, Dr. Curtiss suggested that at least three events must occur in order for this type of risk to occur. First, the organisms must move from one individual to another and infect; second, the organism must be able to establish itself in the individual to cause the disease; and finally, the organism must be able to overcome the defense mechanisms of the host. He indicated that some experiments now completed suggest that the probability of these three factors occurring under the conditions established for DNA work is very low, measurable, but not as likely an event as might be implied by opponents of the research—in other words not an unacceptable societal risk.

Dr. Wald

Dr. Wald, in commenting on Dr. Barkley's statement on laboratory accidents, emphasized that since there is really no routine method for monitoring the transmission of diseases between laboratory and home or community, or for monitoring the health of workers and their families, it is difficult to state that this has never happened. [This is a point made by others concerned with the problem of monitoring the on-going research in laboratories since there is now no standard method procedure.]

C. General Perspectives on Risk/Benefit Analysis in Public Policy Decisions

Dr. Wilson

As Richard Wilson, Physics Department, Harvard University began his testimony, he pointed out that there are some situations where risk analysis is helpful and others where it is not helpful. Where data are available, as in correlating automobile accidents and the reduction in injury by wearing seat belts, estimates of the lives saved by installing seat belts versus the cost of the belts can be provided with reasonable reliability. In other subjects of interest in policy decisions, as in estimating the risk to health from exposure to radiation or chemicals, similar calculations are possible from data on high levels of contamination. It is a much more difficult problem to make estimates with a high degree of certainty when the risk from exposure to low levels or small concentrations is not well defined. The analysis becomes even more uncertain when extrapolations to large populations living under various environmental stresses are under evaluation. The risk to a small population may be small but with large numbers, even low level risks might produce a greater significance since small multiplication factors with large populations can result in danger to an unacceptably large number of human beings; uncertainties as to the degree of risk may be larger. One major difficulty with some calculations of risk-benefit is that very important factors may be left out of the determination. For example, in examining the relative risk of using nuclear power versus coal fired boilers, one might reach a conclusion, as is the case with most such calculations, that an expanded use of coal might produce an overall immediate hazard greater than from the use of nuclear power. On the basis of this determination alone, a policy might be inferred which would lead to a conversion to nuclear power. However, while not related to the immediate health risk calculation, the potential for nuclear war from terrorist acquisition of plutonium from expanded use of nuclear power plants may be a more important factor which must be considered, and this might lead to a conclusion to accept the greater health risk from coal fired plants.

The point of this discussion was to emphasize that risk-benefit calculations frequently do not include all of the factors which must be taken into consideration when making a public policy decision. In addition, the uncertainties of any extrapolation of data from small samples to high populations must be clearly understood by any political group making a policy decision based upon such calculations. Dr. Wilson indicated that he had examined a number of public policy issues and had observed that in many instances public distrust is created by the way in which information derived from risk-benefit analysis is presented. He stated that if it is made clear that risk estimates have been made on the basis of certain listed factors and that other poorly known or unrelated factors have not been included there might be greater public understanding of decisions being made on the basis of the estimates.

Dr. Lowrance

The DNA issue, according to William W. Lowrance, Department of State, fits into the category of those issues where formal risk-benefit analysis probably does not have an application. In support of this ob-

servation, on which Dr. Lowrance is in agreement with Dr. Wilson, he pointed out that DNA recombinant research covers such a wide range of activities, and the long-range consequences of the research are so poorly understood that it is not possible to do more than speculate about probabilities of hypothesized events occurring. Where quantitative data of reasonable reliability are not available it is not possible to do more than speculate; and to convey the impression that an estimate of reliability can be obtained merely through mathematical manipulations does disservice to the concept of risk-benefit analysis. Dr. Lowrance indicated that formal risk-benefit analysis finds its best applications where the elements under analysis can be identified in parallel with real events in the world so that variation in the risk-benefit model can be compared to postulated variations in the real world.

In order for some order to be brought to the examination of the DNA issue, it is important to set a good base line for accumulation of data. The acquisition of information should involve an evaluation of a large range of problems and include the input from a variety of disciplinary studies. Nucleic acid research is not defined well enough today to permit a one-time analysis. In summary, he would suggest a flexible interrelated analysis with a gradually evolving examination as information is made available. Dr. Lowrance would encourage society to set up voluntary restraints and mechanisms for institutional review to prevent improprieties. In his view, this examination has begun as evidenced by the responsible behavior of the scientific community, its willingness to focus public attention upon the problem, and the involvement of many academic disciplines and public interest groups.

Dr. Lowrance added several other points of interest during the discussion of his testimony. As he indicated, DNA research will benefit only a very small group for a considerable period of time. These are the researchers whose lives are invested in unraveling some of the fundamental problems of life. On the other hand, the public perception has been that this small area of research might possibly pose a risk to a large population or the entire environment. Because the research is international in scope, prohibitions on the research in the United States will not prevent any mishap should it occur in some other nation. Since the risks and benefits will ultimately affect the entire world, it is especially necessary to maintain an awareness of all developments so that proper analysis can be completed on a continuing basis as more information is made available.

Dr. Michael

Donald N. Michael, Institute for Social Research, University of Michigan expressed his agreement with the points of view presented by both Dr. Wilson and Dr. Lowrance. He highlighted, however, the need to place any risk-benefit analysis in the social setting in which the evaluation is being made. Social groups will interpret the analysis in different ways depending upon their value judgements of risk or benefit. In his opinion, the social setting has been changing at an accelerating rate and those who perceive a risk in some issue now insist on a greater role in making the final policy decision about accepting or rejecting the activity related to that risk. Dr. Michael

sees the DNA issue as an extremely important episode in the increasing conflict between those who see the right to freedom of inquiry as paramount and those who insist that the public interest is better met by other criteria. The DNA issue may be of particular importance because it serves as a focal point for beginning to learn ways of conducting inquiries in the policy-making process when the data are ambiguous and conflicting, quantitatively as well as qualitatively. Dr. Michael went even further; he believes that the problem of dealing with issues like DNA recombinant research is so complex and is being debated in an atmosphere of so many conflicting social values about what is worth risking and what is worth gaining that even with a beginning flow of data a risk-benefit analysis alone would not be adequate to resolve the controversy.

In further examination of the implications of the irreversibility of effect (from genetic research) which was introduced by Dr. Lowrance, Dr. Michael went on to explain that we simply do not know enough about ecological systems to know whether any corrective actions following an observation of an undesirable change would be of any consequence. With regard to calculations of risk which have been made in defining probablities of failure of ventilating systems or biological containment systems, Dr. Michael noted that we have no way of calculating the likelihood or effect of the interaction of any human errors which would override the control systems imposed by the guidelines. We can be certain that accidents will happen. We can be equally certain that an accident will happen in DNA recombinant research. There is no way of calculating the risk of such an accident occurring or predicting a probability that the occurrence of such an accident would be harmful. As a final point of interest, Dr. Michael discussed the dilemma posed by a more philosophical aspect of the DNA issue by pointing out that we are attempting to determine policy now for an area of research which probably will not significantly affect society for some time; thus, we are presupposing what the society ten or more years from now will envision as acceptable or unacceptable risks. In other words, he was expressing the uncertainty that we might not know a decade from now whether the population might set its priorities such that it would rather spend money on reducing environmental factors identified as correlated with cancer rather than apply a technology which offered a chance to reduce a smaller number of genetically induced defects. A reasonable risk-benefit analysis should attempt to anticipate future values and how risks and benefits might be perceived at that time. He does not know how this kind of determination can be made now.

For these and other reasons, Dr. Michael emphasized that it is important for those involved in making policy decisions to have available a number of analyses made by different groups with different perspectives. Such analyses should clearly identify biases and the bases of determinations including those factors which have been excluded in the analysis as well as those included. He views this approach to science policy determination as a new and learning phase. The inclusion of the examination of values, ethics, and morals in science policy is going to make the task much more difficult than some earlier determinations which were based upon quantitative data alone. A basic issue involved is the right to freedom of inquiry

when an inquiry obviously has implications for society which cannot be clearly defined as entailing no risk. Since science now has a formidable impact on society, it will be necessary for those responsible for establishing science policy to give greater consideration to the social implications of scientific developments.

Mr. Dyson

Freeman J. Dyson, Institute for Advanced Studies, Princeton, is of the opinion that the issue of the right to freedom of inquiry is a false issue in the debates produced by the DNA recombinant molecule research. He believes that those involved in research recognize that society has already exercised some control over scientific inquiry. The problem is really one of how much of a limitation on inquiry is possible without interfering with the stimulus necessary to encourage basic research. Neither does Mr. Dyson agree that the risks of DNA recombinant research may be unprecedented. He suggested that the attempted control of the atomic secrets is an example of a classic failure of society to prevent or control the use of a dangerous technique. Despite some of the most rigorous security methods which could be conceived and implemented, the security system came to be treated with contempt, and the secrets are now held worldwide. He believes that the inflexibility of the controls used in the attempt to control atomic secrets was a primary reason for the failure of this control system. He suggests that a more flexible and humane approach to regulation of DNA recombinant research would be more successful. He would favor legislation which would permit maximum flexibility for the exercise of judgment for both operation and enforcement of controls.

Dr. Michael phrased his concern about present estimates of risks which affect later generations in a different way during the discussions which followed the formal testimony. He indicated that responsible judgments on risks will depend increasingly on estimates of longer range futures. Because of this requirement, there is a need to give more consideration to alternative futures and to make explicit in the analysis which alternate futures were examined in selecting a particular policy. Then, as the future moves closer to reality, reexamination of those analyses will be required so that the analyses may be modified by nearer term data. This would mean, as highlighted by Dr. Lowrance, that the Congress needs to provide leadership in setting priorities. In the case of the DNA issue, this might mean that the Congress would categorize research experiments in terms of potential risk, and also in terms of potential social value. Where the risk is very small, the experiments might be permissible. If there is obvious social value in conducting the experiment (e.g., experiments to determine more precisely what the risks of recombinant DNA research are, or experiments directly relevant to the treatment of disease), a slightly larger risk may be acceptable. If these permissible experiments are carried out and show that the risks are less than originally thought, other experiments, perhaps slightly more risky or having less obvious social value, might then be authorized (e.g., experiments directed towards improving the nitrogen-fixing capabilities of plants where at some time it may be necessary to release new organisms into the environment).

Dr. Cavalieri

In his discussion of the probability values which can be assigned to a potential accident in DNA recombinant research, Dr. Cavalieri suggested that it is impossible to make such calculations. He refers to the hundreds of operations required in such research, each of which could involve some error leading to an accident, and suggested that no meaningful risk-benefit calculation could be made of these processes. Furthermore, some researchers in this field believe that it is possible to characterize a DNA fragment as being "pure", that is, uncontaminated by some unidentified fragment which might be carrying unknown traits. The ability to characterize with precision the DNA fragment which is to be cloned is an important part of the safety precautions being developed for DNA recombinant work. Cavalieri is concerned because of work completed in England which suggests that a "pure" fragment of DNA may in fact contain overlapping information which might code for a second protein other than the one associated with the fragment. In his opinion, the presence of unexpected fragments in a so-called "pure" fragment of DNA introduces an additional question regarding the reliability of the guidelines. He further suggested that the authors of the NIH guidelines had not taken this possibility into consideration during their development of the guidelines.

Dr. Cavalieri also stated that the coupling of a low probability of accident with a high risk event is a value judgment requiring societal and not scientific examination as to the policy course which should be followed. This is one of the factors which led him to his position that the discussions about this area of research should be public and that the researchers should not be making the final decisions about the continuation of the research.

Dr. Whelan

With regard to risk assessment experiments on an international level, Dr. Whelan indicated that the European Molecular Biology Organization is constructing a P4 facility and that this site (in Heidelberg) might be the location of any experiments of this type.

Dr. Cape

In his comments on risk-benefit analysis, Dr. Cape supported the views of a number of other observers. The points he considered most important included: (1) in the assessment of unknown risks compared to benefits, which of these are certain cannot be made by debate, and these uncertainties must be evaluated experimentally; (2) any indication of "diabolical" efforts in genetic engineering, particularly involving human beings, should be prohibited; (3) DNA recombinant research should not be the "whipping boy" for general concern about the impact of scientific developments on society and changes in science policy.

Dr. Singer

During her panel discussion, Dr. Singer indicated that she perceived that there were more areas of agreement than disagreement with regard to the use of the DNA recombinant molecule research method.

There are some types of research with which there is little if any disagreement; that is, experiments within the same species and which do not involve pathogens. There are experiments, prohibited by the guidelines; which all agree should not be attempted until much more information is available, and then there are areas where there is uncertainty and, at least from the perspective of the researchers advocating the research, these should be controlled until more information is available; these are the areas governed by the P2–P4 types of experiments described in the guidelines. Here the issues center more on classification and less on whether the research should be conducted.

IV. SCIENCE POLICY IMPLICATIONS OF THE DNA RECOMBINANT MOLECULE ISSUE

A. Introduction

A principal objective of the entire series of hearings was to focus upon the science policy implications of the issues highlighted by the national and international controversy over the regulation of DNA recombinant molecule research. The Subcommittee wished to consider such topics as: (1) the complex task of improving public participation in scientific and technical decision-making; (2) the action which should or could be taken by the Government to encourage scientists to provide an early warning when new developments with a potential for social impact are in the early stages; (3) the freedom of scientific inquiry; (4) who among the public should be involved in the decision-making process; and (5) ways which might be useful in resolving value conflicts among the various groups who become involved in these issues. It became obvious during the discussions of the role of risk-benefit analysis in science policy that social factors are increasing in importance in the evaluations pertinent to the determination of such policy. The DNA debate produced many relatively unique opportunities for the participation of non-scientists in a public examination of a research issue. The debates also involved a number of professional societies, lawyers, social scientists and ethicists. In order to examine the ideas developed by such individuals, several witnesses were asked to present their views regarding the DNA controversy and to place these views in the broader context of the need to reevaluate past and present procedures in science policy determinations.

B. International Activities

The nature of international proposals for the regulation of DNA recombinant research was discussed by William J. Whelan, Chairman of the Department of Biochemistry, University of Miami School of Medicine. Dr. Whelan is the Secretary General of the International Council of Scientific Unions (ICSU) and the Chairman of the Committee on Genetic Experimentation (COGENE), of ICSU. The International Council of Scientific Unions includes 18 international scientific unions with 64 national members. The Committee on Genetic Experimentation (COGENE) has identified a need for an international, interdisciplinary, nongovernmental, and apolitical group to solve some of the problems relevant to the issues surrounding DNA recombinant research.

There are regular observers at the COGENE meetings from UNESCO, FAO, and WHO. Thus, the international commitment to this problem appears to be rather extensive. Dr. Whelan emphasized that the perspective of COGENE is not to determine whether the research should be banned but instead, recognizing the value of the

research, to evaluate the research for the purpose of insuring safety, and to provide for the examination of the complex, moral, legal, and ethical issues for society that have been highlighted by the debates on this issue.

Dr. Whelan

As pointed out by Dr. Whelan, the DNA issue, which has been likened to the nuclear debates, differs significantly from them. It took almost 30 years for nuclear technology to reach the point where terrorist activity became a concern. In the case of DNA recombinant molecule research, graduate students or others could easily carry out such experiments. The bans established by the NIH guidelines are thus not limited by the need for technological development and expansion as was the case in nuclear issues. Because such capabilities are present in molecular biology, Dr. Whelan agrees with Dr. Fredrickson that there is a need for substantial international cooperation in the development of any standards and guidelines which are to be applied to all areas of DNA recombinant molecule research.

Dr. Whelan noted that ICSU perceives a number of objectives that are desirable. These include: (1) There should be universal agreement on safety guidelines without the compromises of substantial individual exceptions; (2) national and regional bodies acting in this field should have clear and rapid means of communicating with regard to new developments as well as problems; (3) there is a need for wide availability of good training; (4) there is a need to conduct risk-assessment experiments to examine the reality of some of the alleged hazards; and (5) there is a need for a thorough examination of the ways in which industry might use the DNA recombinant technology on a large scale. He concluded his summary of international activities by indicating that he hopes that the United States will not lose sight of the need for international initiatives in examining and resolving the issues associated with DNA recombinant research.

Professor Nelkin

Dorothy Nelkin, Program on Science, Technology, and Society, Cornell University, was able to offer the results of some of her observations on efforts in Europe to broaden public participation in science and technology policy. She discussed work in Sweden, the Netherlands and Austria where experiments had been initiated in several areas with a primary emphasis upon public concern about nuclear power issues.

In Sweden, the government sponsored experiments in public education concerning energy policy. Within their adult education programs, several thousand groups of about 15 persons per group participated in meetings to discuss nuclear energy policies. These study groups provided an opportunity for about 80,000 persons to examine this issue. Sponsoring organizations were provided with government assistance to develop materials which reflected the social and political interests of their members. Although government officials had anticipated that such discussions would alleviate concern by providing for effective dissemination of information, the surveys of the programs suggested that prior attitudes persisted and it is possible that there

may even have been an increase in uncertainty and confusion. Ms. Nelkin reported, however, that the Swedish surveys did suggest that the programs may have abated some of the hostile antinuclear activity.

A different approach to the antinuclear protests was taken by the Netherlands government. In that country, the Minister of Physical Planning set up a system requiring publication of all policy intentions before physical planning could proceed. [In some respects, this program sounds like one of the objectives of the U.S. Environmental Impact Statement requirements.] The Dutch policy objectives publications were intended to address such issues as economic growth, project objectives, and impacts, and were circulated for public comment. The public response was then evaluated by a representative council with members from worker groups and voluntary organizations. Hearings were held to examine the public comments. The results of the hearings were then publicized to insure that the original intent of the responses had not been modified by the council. The final response was provided to the Minister who had to respond or change the plans, with the Parliament making final decisions.

According to Ms. Nelkin, the Austrian approach was somewhat analogous to the U.S. "science court" concept. In Austria, the Minister of Industry constructed lists of questions which had been solicited from the opponents of nuclear power. Teams of experts representing both pro and con positions then prepared for and conducted televised debates. The Ministry prepared informative background information for public distribution preceding the televised debates to assist in the understanding of technical terms. Public response was solicited, and then a report was prepared to summarize the issues which had been resolved and those which remained controversial. Ms. Nelkin indicated that, as in Sweden, conflict still remained although it was the hope that public examination of the issues would enable the public to see more clearly the limits to the expert opinions on both sides of the debate.

These special attempts at involving the public in the nuclear debates were accompanied by a number of other efforts in all three countries. For example, special efforts were made to involve consumer groups in an assortment of government councils and outside evaluation groups of various kinds were invited to participate. Ms. Nelkin summarized the conclusions which appeared to be most obvious from these experiments. First, science policies are intrinsically controversial, and the furnishing of technical information is not sufficient alone to resolve conflict or change public attitudes; however, the participatory process does serve to bring better focus to the issues of concern and may serve to reduce hostility and polarization. Second, the use of experts is a crucial political resource. Public access to technical experts must be improved. Third, the values derived from public involvement must be carefully examined. The balance between the need for public involvement and the possibility that the decision process may be slowed or made more complex must be carefully examined. Despite all of these cautions, Ms. Nelkin indicated that there is little doubt that the desire for public involvement is spreading and, as indicated by the high level of interest in DNA recombinant research, even basic research is not immune to public examination.

C. Public Participation in Science and Technology Decision Making

(1) *Scientific Societies.*—Scientists all over the world are organized, usually by specific discipline, into associations or societies for purposes ranging from the need to have a common forum for the exchange of new developments, to the more recent phenomenon to have a community of effort for strenghtening involvement in public policy determinations. The effectiveness of these organizations in determining science policies has been a matter of interest for some time. Representatives of several of these organizations were asked to discuss the manner in which they are responding to the expressions of interest in participating in public policy matters. The Federation of American Scientists, with long experience in the debates over nuclear power, has developed a number of techniques for gaining participation by scientists in policy matters.

Dr. Stone

Jeremy Stone, Federation of American Scientists, stated that he could summarize five lessons which could be learned from the DNA issue. These are: (1) There were enough researchers engaged in this field with a sense of public responsibility to direct attention to the issue very early in the work; (2) many of these scientists were willing to confront the issue in public, and since it is difficult to clearly define the dangers, it has taken great courage to discuss the problem in a highly emotional and speculative atmosphere; (3) the history of the issue shows that it is extremely difficult to stop such research—since it is international in scope it would have gone forward even if the United States had banned the research; (4) the issue is unusual since it is the research which is considered dangerous and not just the following technological development which is usually the case; and (5) even though it may appear otherwise, the scientists should take encouragement from the fact that the public reaction thus far has been restrained.

Dr. Stone indicated that for most scientists, being socially responsible means avoiding "irresponsible conduct." Actually, the Federation view is that scientific responsibility means "social responsibility." Since there appears to be only a minority of scientists willing to take the time to become involved in issues of social policy, the Federation has suggested several actions which the government might take to encourage greater participation by scientists. Dr. Stone suggested that political bodies, like the Subcommittee, might ask the scientists in a formal way what is going on; take a little more time to listen to those scientists who respond; make it financially feasible for scientists to speak up; and commend scientists who do take the time from their research to enter the public policy debates which center on scientific issues. After a discussion of several of the ways by which the government already fosters public participation in lobbying efforts through the structure of the tax laws, Dr. Stone indicated that still more needs to be accomplished. Although the Science for Citizens concept being addressed by the National Science Foundation is a step in the right direction, there is always a tendency to direct such efforts more toward education in science rather than education about the implications for society of scientific developments. It is this latter point which Dr. Stone indicates needs more support. By recognizing the efforts of

scientists who provide direction and lead such efforts, by commending those who are willing to speak out on controversial issues and "condemning" those who do the wrong thing, the Government could encourage scientists to take time away from research as necessary to insure public understanding of the implications of their research. It is also necessary that ways be found so that scientists themselves become more sensitive to the social implications of their research; then, they can take steps to force examinations of these issues. This sequence of events has happened in the case of the DNA recombinant molecule research issue.

Mr. McGowan

Alan McGowan, Scientists Institute for Public Information, had been involved in other debates on the DNA issue and provided his reaction to the issue. He believes that the key to all future issues which must be confronted by the scientific and public policy bodies is information. The scientific controversy over the past several years has resulted in a much better informed public with regard to the DNA issue than is usually the case so early during the development of an important scientific issue. Since the public is already involved in determining research priorities because it is public money funding such research, there is every justification for the public to be fully informed when issues such as DNA recombinant research arise. The scientific method provides for the resolution of the conflicts which arise during scientific disagreement. Questions are asked, experimental evidence pertinent to these questions is collected, the evidence is evaluated by peer review, and the questions revised to ascertain the direction in which new experiments should be conducted. Mr. McGowan believes that the scientific method is a good framework for public debate. The facts need to be clearly discussed, the areas of uncertainty defined, information collected if possible to eliminate questions, and there should be a continuous, informed, open debate about the issues as the facts change. Acrimonious debate disrupts the course of such discussions and often leads to a political confrontation which does little to resolve the debates.

Mr. McGowan offered a proposal for the establishment of a national commission on biomedical research to serve as a forum for open public discussion and debate in a formalized manner of issues such as DNA recombinant research. Such a commission could: (1) have the capability to develop an independent information service; (2) convene public hearings; (3) encourage lay and professional citizens to question and comment; (4) develop educational materials; and (5) initiate international discussions for areas where national boundaries are not a primary constraint to the conduct of such research. Such a commission should be composed of scientists, businessmen, labor representatives, and the various public sectors.

Dr. Trumbull

Richard Trumbull, Executive Director of the American Institute of Biological Sciences, then summarized some of the ways that the AIBS attempts to provide for scientific participation in public policy issues. Like several of the other speakers, Dr. Trumbull indicated a need for continuing educational programs for both scientists and citizens. According to Dr. Trumbull, it will never be possible to get

maximum informed public participation if the task of information evaluation is impossible for the lay citizen. Dr. Trumbull referred to the many attempts to gain public involvement at the local, State and Federal level as a major sociological experiment requiring intensive evaluation by social scientists. For example, at the very time when there is a growing awareness of the need to obtain informed public participation in government policy, there are counter efforts to reduce public involvement and education. He cited the current efforts to reduce public participation in Federal advisory committees, efforts to reduce expenditures by Federal agencies on public education, limitations of information retrieval systems to Federal use only, and generally limited examination of public involvement in science policy issues by congressional committees. Dr. Trumbull noted that there is a lot of activity going on now that is productive but needs to be constantly examined, reevaluated, and restructured as necessary to achieve the end of informed citizen involvement in the determination of science policy issues. Most of the large scientific societies now have professional activities to provide for participation by scientists in on-going public policy issues. Organizations such as the AIBS have congressional liaison staffs, newsletters, special committes, and special programs at their meetings to provide for the dissemination of information and to support discussion and debates about issues in science policy.

As emphasized by Mr. McGowan, however, it is necessary to keep in mind that there are many publics, and many types of conflict. It is unreasonable to think that education alone will solve all of these problems. There will always be conflict simply because of the enormous range of different values which citizens hold. Further, different perceptions of education often further confuse the issue. Scientists often think that an appropriate level of education has been achieved only when the citizen becomes sufficiently knowledgeable to be a scientist. The scientific community often expects the press to learn the rules of science but won't take the time to learn the rules of the press. There has to be compromise on all sides with meaningful dialogue flowing continuously.

In his summary statement, Dr. Stone pointed out that the public debates on issues become serious when the facts are not well known. The Congress then usually becomes involved in such controversies and must make judgments that are often based upon determinations other than a weighting of the accuracy or inaccuracy of the scientific facts relevant to a particular area of research. The search for political solutions is frequently based on evaluations of factors separate from the search for scientific fact.

As Dr. Stone noted, the real problems may appear as issues which have never been considered. Thus, an appropriate posture would be to deal legislatively with the immediate problems but retain the flexibility to make changes as the issues become clearer.

One point on which all of these witnesses expressed concern was the fact that care must be taken not to create an atmosphere of discouragement for scientists who do take time to participate in research issues that are of public policy significance. There is a tendency for scientists who become involved in such debates to be placed in defensive positions. This tends to create pressure situations among their peers which

decreases the desire of such scientists to participate in other public policy discussions. Unless such scientists see some tangible benefits or favorable recognition from their efforts to be become involved in public debate, there may be a tendency for them to avoid such issues. For example, it has been said that some of the scientists who first brought attention to the DNA issue have been so overwhelmed in public debates involving speculative issues and methodologies which they cannot accept, that they have hinted at the fact that they are sorry they became involved at all. These scientists pay a heavy price for the time taken away from their research to assist in the public discussion. Additionally, these scientists must not be threatened by job loss or other censuring response for their involvement in public policy issues.

2. *Public Interest Groups and Universities.*—During the course of the past few years, a number of citizens' groups have entered the public debates concerning the need for regulation of DNA recombinant research. These groups often were organized as outgrowths of local public interest groups as well as within the framework of more formal local government or university committees. Since participants in this issue have expressed both pro and con positions with regard to Federal preemption of local prerogatives, the evidence from actions at the local levels is of interest. Further, the emphasis (particularly by scientific societies) upon the need for education of both scientists and non-scientists to improve public participation in public policy issues suggests that an examination of these many public forums on the DNA controversy might reveal some base line of competence already available.

Sheldon Krimsky, Associate Director, Program in Urban, Social and Environmental Policy, Tufts University, was a participant in the "citizen" committee in Cambridge which examined the issue of whether DNA recombinant research should be permitted in that city. He summarized three basic points in his remarks.

First, he believes that the city would never have been drawn into the controversy formally if it had not been for the efforts of a small group of concerned scientists. It was his opinion that these scientists risked ridicule and possible setbacks in their careers by directing attention to the issue. He supports the comments by other witnesses that there needs to be a better process of insuring protection for such advocates so that dissident scientists may feel free to speak out on controversial issues. Again, education and training of scientists to heighten their sensitivity and responsibility for public policy issues was suggested as a possible area for strengthening.

Dr. Krimsky

Dr. Krimsky indicated that the citizen board which met to examine this issue demonstrated that it was possible for non-scientists to become sufficiently well informed on technical developments to reach an understanding of the issues. The citizens' group functioned in much the same way as a jury might and also was somewhat analogous to the concept associated with the idea of a science court. The Cambridge committee met with scientists who explained the technical details, listened to advocates on both sides of the controversy, asked for additional details from experts around the country as needed, and then

reached its conclusions and recommendations. In this case, the committee decided to recommend that experimentation be permitted to continue with the addition of a number of requirements. These added to the statements in the NIH guidelines but dealt primarily with administrative controls of the research and not with changes in the basic protocols for the conduct of the research.

Although a science court might be perceived to be analogous to the "citizens' court" type of procedure actually followed in Cambridge, Dr. Krimsky believed that a science court could not have succeeded. In his opinion, and the testimony in other portions of the Subcommittee's hearings tend to support this opinion, there is no single body of fact or theory relevant to the assessment of risk on which all scientists could agree. Accordingly, Dr. Krimsky believes that a broader examination of the problem by a selection of individuals with diverse backgrounds and representing a range of social values should be utilized so that a maximum of public confidence in any decisions could be developed.

Among the issues highlighted by the Cambridge review, Dr. Krimsky believes that several remain unresolved and require more attention. One of these is the need to examine the social and ethical consequences of DNA recombinant research. Since these consequences involve an examination of what, if any, limits need to be placed upon research and the decisions may be far reaching in impact, such a dialogue should be national in scope. In the case of the Cambridge Review Board, a recommendation was made that two national commissions be created. One of these would establish guidelines, health monitoring standards, and licensing procedures for all institutions undertaking recombinant DNA technology; the other would consider the social and ethical implications of the use of the technology in research as well as in industrial and clinical applications.

Mrs. Taft

Hessy Taft, Princeton, New Jersey, also participated in a citizens' examination of the DNA recombinant research issue. She is a member of the Princeton Citizens' Committee on Biohazardous Research. Although trained in science, Mrs. Taft is not currently engaged in DNA research. She shares the opinion evident in Dr. Krimsky's testimony that society can profit greatly in examining public policy issues by using the resources available from local involvement. She expressed the additional opinion, however, that it does little or no good for a local community to insure that safe conditions are established if such conditions are not similarly upheld on a national level. She indicated her belief that there is a need for Federal legislation in this area. Her position was summarized as a need to proceed cautiously but not to prohibit research. She would support continuation of the research only if appropriate precautions are taken and if the guidelines and their modifications can be legally enforced in an effective and practical manner.

Like Dr. Krimsky, Mrs. Taft also believes that there is a need for a continuation of the examination of the larger societal issues that have ethical implications. Again, where it is not possible to quantify the data available, and where contrasting viewpoints are presented by equally competent scientists, the non-scientists must use other value

factors to reach a position of social responsibility. She perceives a need to separate those developing the regulations from those who will enforce the regulations. Further, she does not feel that it is proper for individuals engaged in the research to be a part of the group establishing the regulations to govern the research. Mrs. Taft believes that it is important for local communities to remain involved in the regulation of on-going research taking place in their community.

Dr. Wheeler

Albert Wheeler, Mayor, City of Ann Arbor, Michigan, was in an unusually unique position. Not only is Dr. Wheeler the political leader in a community in which a large university is carrying out DNA research, but Dr. Wheeler also is a member of the scientific faculty of the university. Thus, he had an opportunity to see both sides of the debate. Dr. Wheeler stated without equivocation that he believes that because there are more than just scientific issues involved, it is necessary to have a number of voices represented in the discussion of public policies relevant to scientific research. From its own examination of the DNA recombinant research issue, Dr. Wheeler indicated that the Ann Arbor City Council has determined that it indeed does have a social responsibility in this area. The activity between the City Council and the university research community has increased, and the advisability of requiring the university to provide notification of on-going development is being explored. The net result of all the council's activities thus far has been similar to the efforts of the citizens' committees in Cambridge and Princeton. With only minor recommendations for changes, usually administrative in nature, the council reached the conclusion that the research should continue with adherence to the NIH guidelines, establishment of biohazards committees and similar provisions. Dr. Wheeler expressed the view that the local government's prerogatives should not be usurped, either by the Federal or State government. He believes that citizen involvement in this issue thus far has resulted in a temporary state of "peaceful coexistence."

In order to prevent complete chaos by autonomous local controls, Dr. Wheeler suggested that more effective use of mechanisms for information exchange such as the Mayors Conference, the Governors Conference, the National League of Cities, Counties and Townships, and others could be used to secure Federal and State interchange of ideas on science policy matters.

Dr. Wheeler also indicated that there is a need for the local communities to have ready access to information concerning health and related issues when research problems are under consideration. He feels that ready access to such information is essential in order for both public officials as well as the general public to have an opportunity to examine the facts relevant to such issues. It is necessary to have candid and understandable sources of information immediately available on both sides of any debate. Like the many other local examinations of the DNA issue, it was necessary for the Ann Arbor group to spend considerable time becoming educated before a politically acceptable decision could be generated. It became obvious, as they talked to many of the same witnesses used by other communities, that much time and expense could have been saved if a central source of basic data could have been made available.

Dr. King

Johnathan King, Department of Biology, MIT, also testified on his experiences. He is a member of a citizens' advocacy group that was instrumental in directing public attention to the DNA issue. He is an investigator in the field of molecular biology, often funded by Federal funds, and is quite familiar with the scientific background. He highlighted the problems encountered by a scientist attempting to secure public evaluation of an issue believed to have social implications not generally perceived outside the scientific community.

Dr. King expressed his opinion that up until the Cambridge committee's examination of this issue, there had been no true public involvement. Preceding meetings, in his opinion, either had restrictions formally established by invitation lists or were held under circumstances which prevented participation by a number of concerned individuals. In fact, Dr. King expressed the view that a national policy had been made to proceed with the research without having had any evaluation of the issue by the people's representatives; that is, the public congressional hearings on regulating DNA research were initiated after the publication of the guidelines authorizing the research. This produced a great deal of frustration on the part of individuals like himself who felt that the issue was out of their control. Dr. King thus viewed the decision by the Cambridge City Council as a very important return to the political process.

Some of the accomplishments of the Cambridge Council which Dr. King enumerated as being significant were: (1) they invited public testimony from the opponents of the research; (2) they invited testimony from workers other than the researchers in the laboratory; and (3) they raised the critical questions of accountability and environment. In his opinion, this was the first time that these points were addressed in a truly responsible fashion. He viewed these council meetings as an outstanding example of participatory democracy and an illustration of the fact that people can understand a difficult scientific problem and reach reasonable decisions when they are personally involved in the decision-making process. Dr. King considers local action as the best way to gain public participation. Although he believes that a national commission should be established to examine the DNA recombinant research and other similar issues, there is no reason why the State or local community should not become involved. In fact, he suggested local commissions may even contribute to the work of national commissions. As with Dr. Krimsky's observation, Dr. King believes that multiple inputs to the social implications of science policy decisions may be the best method of resolving such issues. National health policies need to be reconnected to health research priorities. The people should be involved in these determinations.

In direct response to the question about "who decides" in public policy issues, both Dr. Lowrance and Dr. Michael indicated in their testimony that the decision process should be and is a process in which the public has a right to participate. The public, as they envision this process, includes the Congress, through its representative role, through the committee hearings and similar forums; and public discussions at the local level. The determination of the level at which this involvement should occur for specific problems, or the point

at which a decision can be made with a reasonable certainty that a majority of concerned parties have had an opportunity to be heard, is a more difficult problem to resolve. In the case of the decisions regarding the regulation of DNA recombinant research, Dr. Michael voiced the view that the level is wrong. It is a worldwide problem but it received its primary public focus at the local level and then at the Federal level. Although other nations are considering the problem there is no solid international program which would permit a worldwide decision-making process that satisfies the social concerns of all nations. Although there is no way of imposing international law on DNA recombinant research, Dr. Lowrance believes that the beginning efforts of all Federal agencies to work with international organizations could serve to increase sensitivity to such issues. Such discussions at least have isolated agreement that the issue is important and warrants a coordinated examination even though the solution may not be standard in each nation.

Dr. Wengert

Norman Wengert, Professor of Political Science, Colorado State University, commented on his experience in studying issues of policy development and control. As he pointed out, public participation can mean many things. In some instances, it is a matter of good policy because it represents democracy in action. In other instances, it is a strategic use of the public to support a particular position. (On occasion, as pointed out by Ms. Nelkin, public participation even while increasing the level of knowledge does not resolve conflict while in other instances, public discussion and dissemination of knowledge does reduce conflict.) For some members of the public, the opportunity to participate in public discussion of issues is a form of therapy.

In spite of all of the efforts which have been made, Dr. Wengert is still of the opinion that we are not doing a successful job of educating the average citizen to cope with debates involving scientific issues. He believes that there is a need to find some way of exposing students to the policy dimensions of science, as contrasted with the teaching of the processes and techniques of science. There is a need to develop an analytical and questioning attitude on the part of students about the facts which are presented to them in their courses of study. Dr. Wengert cited a number of examples to illustrate how it is often difficult even for scientists to be heard by other scientists if the ideas being proposed are controversial in terms of existing data. If scientists have such a hard time among themselves in keeping an open mind about new ideas then it should not be surprising to discover that the lay citizen has a difficult time in establishing a reasonable position on scientific issues on which scientists cannot agree.

Dr. Wengert mentioned several factors which are related to information processing and scientific policy development. These include: (1) peer review; (2) such laws as the Freedom of Information Act; (3) more attention to the timing of the release of public statements concerning new developments (often premature release of new ideas which are later disproved or which cannot be replicated produces unnecessary public reaction); (4) an improvement in the communication of information to the public through the news media; and (5) the possibility of supporting a public office of some sort to serve as a focus of public input on policy issues.

Professor Nelkin

In one of the concluding statements, Ms. Nelkin indicated that there is a need for social innovation to create a better form of public understanding and appropriate means of accountability for actions. In her view, this is an important part of maintaining democracy in a technological society.

Ms. Nelkin suggested that the issue should not be to attempt to determine or judge hypothetical risks but rather to try to determine the kind of controls which should be exercised until more data are available; it seems improper to regulate the research scientist in his university laboratory and not the commercial scientist in industry as long as this uncertainty about risk remains. It may be wise to avoid overly detailed requirements at this time if general guidelines are adequate to address the obvious areas needing regulatory control.

V. LEGAL, MORAL, AND ETHICAL ISSUES

A. Introduction

It appears that many of the issues associated with the DNA controversy are not amenable either to risk-benefit analysis or to the use of the scientific method for ascertaining accuracy or validity. There is a general impression that the more difficult aspect of national policy determination is one of evaluating the intuition of experienced scientists as opposed to the value judgments of both scientific and nonscientific participants in the debate. However, there also has been an element of concern as to whether there may be some inherent "right" to freedom of inquiry which is being threatened by the proposals to control DNA research. This latter point is of marked interest despite the evidence of instances in which research has been regulated or controlled, albeit indirectly in many cases. In order to gain information on both the extent and nature of the value judgments as well as legal perceptions regarding the rights of the researcher, the Subcommittee examined these more philosophical aspects of the DNA issue.

B. Patent Policies and Other Legal Perspectives of Concern

Mr. Morton

W. Brown Morton, an Attorney at Law, Washington, D.C., provided an opinion regarding patent law as it might be applicable to the DNA recombinant technique or its products. As he pointed out, the patentability of inventions depends upon concealing the nature of the subject of the patent until the appropriate applications have been filed. He told the Subcommittee that it does little good to refer to the one year "grace" period following first publication of research as provided in U.S. law when such information is not restricted by patentability through the laws of other countries. The net result is that foreign patents go to the person who first files. This means in practice that secrecy must be maintained until a U.S. patent is filed. In addition to the need for patent protection, Mr. Morton told the Subcommittee that trade secrets require protection in order to foster business interest in developments, and there is an allied need to protect the proposals of researchers from premature disclosure to other candidates during review of grant applications. Mr. Morton said that the Freedom of Information Act has proved troublesome in its application because of the potential for risks associated with these three areas where secrecy is needed. Mr. Morton referred to the Report of the President's Biomedical Research Panel, June 30, 1976 for a more detailed discussion of these issues. The need for protection of potentially patentable

information and for trade secrets are both issues on which industry has expressed concern with regard to the NIH guidelines on DNA recombinant research. On the other hand, opponents of such research have indicated that secrecy would conceal the very risks with which they are concerned.

Mr. Latker

Norman Latker, Patent Counsel for the Department of Health, Education, and Welfare, also reviewed the issue of patent applications as they would apply to DNA research. At the outset, and in reference to some public suggestions that the Patent Office might be able to enforce the NIH DNA guidelines on commerce by withholding patents for failure to follow these guidelines, Mr. Latker testified that he believed that this would be a less than effective control system. He preferred the continuation of the policy of permitting universities to own their inventions and then to collaborate with the industrial sector for commercialization of such inventions. However, he does not believe that licensing control is an appropriate method for controlling commercial compliance with the DNA guidelines. Mr. Latker was concerned that there appears to be insufficient recognition of the difficulty of commercializing new developments and that any further complication of the patent process or forced premature general public access to patentable information might further delay commercial development of valuable ideas. Mr. Latker made reference to data available which tend to indicate that patented developments owned by the Government fail to move into the commercial market because of the difficulty in obtaining risk capital in ventures where there is no assurance that patent protection will be maintained to protect the investment.

Mr. Anderson

Rudolph J. Anderson, Jr., Associate General Counsel and Director of Patents, Merck and Company, addressed the same problem of the need for protection of risk capital in order to stimulate investment in the development of new ideas. He emphasized that Government regulations and laws have a direct influence on private research investment. He believes that a basic factor in the U.S. industrial system is the protection of freedom of competition and that the patent system serves to protect this freedom. The reward for effective competition is the profitable sale of a new product. The patent system assures that society does not have to pay for industrial development, stimulates other manufacturers to search for other routes to solve problems (often less expensively and more effectively) and makes it unnecessary for society to select research projects to be funded. The patent system also produces pressure on a manufacturer to commercialize a valuable development as soon as possible. Although Mr. Anderson believes the HEW position on patents obtained through Federal funding within universities has been useful in stimulating commercial development of federally funded inventions, he has some concern about patents obtained through Federal funding of research in private companies. Proposals to control patents through mandatory licensing of rights under federally developed research, he views as inimical to rapid commercial development. Mr. Anderson pointed out that the British have now recognized the deficiencies in compulsory patent licensing and are eliminating this practice with regard to drug patents.

Professor Newburger

The National Science Foundation has supported a number of studies of factors associated with the development and commercialization of ideas developed under Federal research funding. David J. Newburger, School of Law, Washington University, completed two projects for NSF which involved an examination of the questions of regulation and innovations in chemical and allied products industries. As he views the DNA debate, there appear to be two policy problems. These are: the possibility that public and worker health and safety might be endangered; and the possibility that research and innovation might be curtailed unduly by regulation. According to Mr. Newburger, the science policy dilemma is to solve both of these problems simultaneously. In his opinion, in order to do so, the Government should provide the regulatory agency with the right to develop flexible enforcement devices and appropriate penalties. However, in order for such an approach to work, those affected, such as the developers of new processes, must have a clear understanding as soon as possible as to what these regulations will be.

Mr. Newburger noted that one step in the enforcement of the desired conduct of research would be to construct licensing requirements which: prohibit unqualified individuals from engaging in the research; require licenses for people who are to engage in the research and assure their competence; and, control the sale of the substances needed in the research, such as the restriction enzymes, in order to limit the unauthorized conduct of research.

The issue of Federal preemption of local authority was addressed again by the participants in this panel just as it had been touched upon by other panelists. Opinion continued to be mixed, however. If a trend could be detected at all, it seemed to be one of preference for Federal preemption in order to insure national standards. One suggestion which seemed acceptable would be to establish Federal standards with the local biohazards committee having the authority to determine the adequacy of a particular local facility to conduct the research. Thus, while Federal standards would prevail, local communities would have an input to certification of facilities and determining whether appropriate levels of containment are being utilized in conformance with Federal requirements. Most panelists seemed to feel that some chaos might ensue if local communities had freedom to accept or reject Federal criteria established for a specified kind of research, as with DNA recombinant research.

Mr. Singer

Daniel M. Singer, Attorney at Law, Washington, D.C., suggested that the more elaborate the bureaucracy for regulation, the higher will be the price paid in discouragement of research. The minimal requirements necessary to secure a reasonable degree of research safety could be met by two requirements: Certification that an institutional biohazards committee is established, as specified by the NIH guidelines, and delivery to a central registry of approved proposals. It might also be desirable to provide for a 30-day evaluation period at the Secretary of HEW level for proposed P3 work, and possibly a statement of affimative approval at the Departmental level before P4 work could be initiated. In Mr. Singer's opinion, the construction of a Federal bureaucracy to license individual investigators, to review

and approve each project, annual or other renewal of licenses, and similar detailed requirements would substantially discourage recombinant DNA research

C. Constitutional Issues of Concern to Basic Research Considerations

Professor Barron

In the session on these issues, Chairman Thornton observed that it would be useful to compare the constitutional basis for freedom of expression with the right of Government to regulate action. Jerome A. Barron of the National Law Center, George Washington University, emphasized that his examination was directed primarily at what first amendment protection means in terms of scientific research. He refined the issue for discussion purposes as a question of whether constitutional law (as evidenced in case history) has accepted the idea that the pursuit of scientific knowledge is protected wherever the pursuit may lead. Professor Barron indicated to the committee that there have been some broad interpretations from the Supreme Court which might suggest a sort of blanket protection for scientific research.

In discussing several of the precedents which have been examined, he referred to the constitutional right to receive information and ideas. As he explained the issue further, however, it seemed less clear that, if there is indeed a right to receive, that this right automatically supports the right to explore and investigate. Using several cases related to the issue of obscenity, he pointed out the paradoxical nature of the various arguments as they might be applied to an examination of the freedom to inquire through basic research. For example, would the final decision be left up to local community action as is the case in obscenity determinations? Professor Barron apparently believes that special attention is given to first amendment freedoms because this amendment is a structure favoring change. Scientific research contributes to change. Obstacles to change are of concern. Therefore, if the irreversibility of potential changes from such research as DNA are indeed true, they provide difficult issues for examination from the perspective of typical constitutional protection of freedom precedents. Because of the very specialized and controversial nature of the DNA debate, Professor Barron indicated that certain basic propositions should be kept in mind. These are: first, claims of pure scholarship and an unlimited right to communicate have rarely been examined by the Supreme Court in absolute terms; second, a first amendment resolution to the problem of permissible societal limits of DNA research will be futile if a clear decision for or against uninhibited DNA research is sought; third, if first amendment doctrine is used to solve such problems as limits of scientific research, it will serve only to mask rather than clarify what is taking place; and, fourth, if first amendment tests are to be used in the DNA issue, then a clear balancing of pro and con arguments (risks-benefits) is necessary. Mr. Barron perceives the issue as one of determining how many people in society should share in decisions which might conceivably result in reshaping the nature of life. A claim to the right of free inquiry should not be used to shield science from participation by the public on matters which could be of profound significance to all.

In his concluding remarks, Mr. Barron noted that the first amendment provides as much case law which would support the proponent in the DNA controversy as there is to support those who oppose this research.

Professor Berns

A political scientist, Walter Berns of the University of Toronto, has had an interest in constitutional law, and more specifically the first amendment to the Constitution, for some time. He considered DNA research to pose questions of whether such research might be considered a form of speech and thus protected by the first amendment. He believes that if this question had been asked in the past the answer probably would have been yes to both parts. The historical assumption, according to Professor Berns, has been one of viewing science as good for society, and because absolute freedom was good for science, absolute freedom of inquiry was good for society. Today, however, Professor Berns notes that there are some scientists who are beginning to have doubts about science's value for society and there is an even larger segment of the general population with doubts concerning the net benefit of science. He perceives that the time for more caution in scientific reseach is being enunciated by new social forces. Under these circumstances, he would see nothing in the Constitution to prevent the Congress from exercising its prerogative to require a new degree of caution in the process of scientific inquiry. He perceives nothing in the first amendment to forbid the Congress to address the question of scientific research from the point of view of its good for society rather than from the point of view of individual rights. Mr. Berns focused a considerable portion of his thesis around his view that there may be an increasing need for man to move slowly in whatever capabilities he may have to modify man. Associated with this concern was a suggestion that Congress may wish to consider the construction of a constitutional procedure for encouraging discussion of the societal issues which have been highlighted by the controversy centered around the DNA recombinant molecule research issue.

Professor Emerson

A somewhat different position on the constitutionality of the right to freedom of inquiry was summarized by Thomas I. Emerson, Emeritus Professor of Law, Yale Law School. According to Professor Emerson, the first amendment lays down fundamental principles which should be applied in any examination of the freedom to conduct basic research. He cautioned, however, that while the first amendment could be interpreted as providing full protection for expression it does not necessarily offer the same protection for action. This "separatist" view of the first amendment suggests that scientific research might need to be analyzed to determine the phases of the research which may be identified clearly as expression and those portions which are action. According to Professor Emerson, expression is fully protected by the first amendment. Action is, or may be, subject to regulation, although regulation must conform to due process of law as to equal protection and other constitutional requirements. In the case of the specific issue of DNA research, Professor Emerson suggested that the study of the theories involved and an exposition of these

ideas and theories could be identified as expression. On the other hand, the classification of experimentation which seemed to threaten the public health might possibly be considered as action, and thus subject to regulation.

With regard to the classification of experimentation as action, Professor Emerson suggested that undoubtedly there would be some experimentation which would be expression since the experimental method is so much an integral part of scientific inquiry. At the same time, when experimentation can clearly be identified as having the potential for harming the public health or safety, then such experimentation probably would fall within the category of action subject to regulation. He recognized that there would be a large gray area in which the clear identification of this transition from expression to action would be difficult. In fact, this matter is the subject of much debate between those who perceive little or no risk in recombinant DNA basic research and those who see great potential hazard.

Protection of Ideas

Thus, Professor Emerson suggested that the theoretical development of DNA research and the discussion of the ideas associated with such research are fully protected under the first amendment and any attempt to control or prohibit such research would be unacceptable. Any attempt to prohibit or impose restrictions on thinking, talking and theoretical development would be unconstitutional. He did indicate, however, that there are instances in which the Supreme Court has not exhibited agreement with his perspective of the first amendment and he cited several cases to illustrate this departure from his analysis. The doctrine which Professor Emerson believes should be applied to any examination of first amendment issues in scientific research is a structured balancing test composed of two elements. The two elements of the doctrine described by Professor Emerson are: compelling reasons; and "least drastic means." By this, he meant that the burden of proof should be on the Government to show that there is a compelling reason for regulation, and second, that the Government should use the least drastic means possible to achieve the objectives of the regulations. For example, a compelling reason would be an indication of a serious danger to the public health. The least drastic means would include such considerations as temporary regulations rather than permanent regulations; limited restrictions rather than prohibition; if licensing is not required, do not license; and other similar examples. Professor Emerson also believes that once the determination is made that regulation is required, these regulations should be established by a single source, in this case, Federal regulations. Regulations by States or local communities could result in suppression of scientific information and would not be considered the least drastic means. Finally, in any instances where regulation is determined to be required, there should be strict procedural safeguards. He referred to these procedures as first amendment due process and indicated that such processes would be particularly applicable in any regulation of scientific research.

Unlike Professor Barron, Professor Emerson indicated that the courts have a very important role to play in the public examination of such issues as have been highlighted in the debates on DNA recombinant research. Professor Emerson expressed his agreement with

Professor Berns' suggestion that there is a need to establish a social apparatus for the decision-making process which provides for an unbiased and nonpartisan examination of first amendment issues. There is further a need to isolate such problems as the DNA recombinant research controversy so that they can be examined in as unemotional and rational an environment as possible.

Professor Green

Harold Green of the National Law Center, George Washington University, has been involved with an examination of the DNA issue almost from its inception. Professor Green expressed his view that the problem of whether the research was protected by the first amendment was not clearly defined. It had not arisen in the context of court examination of such issues but apparently had derived from the concern of a number of scientists that their right of freedom of inquiry was being inhibited by the public inquiry and proposals to limit this area of research. A few of these scientists had expressed the concern that the move to regulate biomedical research might even be interpreted as a beginning of regulation of all basic research. Because the issue has been highlighted by concerned scientists unfamiliar with constitutional law, such distinctions between freedom of expression and actions which might affect the public health have not been clearly enunciated. Thus, much confusion has entered the public discussion on the approach to regulation represented by the development of the NIH guidelines.

Professor Green suggested that there even may be some confusion in the minds of concerned scientists as to whether the argument is over the constitutional right to freedom of inquiry or whether it goes to the "right" of the scientist to public funds for research. Are these two issues, in fact, the same? He considers that the right to freedom of inquiry at this time is, in itself, unusual because of the knowledge held by scientists of other instances in which research has been regulated by the Government. These precedents for regulation of research are evidence, he thinks, that the potential for regulation of DNA research is well established in the case history. Thus, Professor Green tends to the view that such discussions correlated with the DNA issue are more political in nature than they are true examinations of the constitutionality of the issues under consideration. In his concluding remarks, Professor Green saw a paradox in his allegation that scientists feel free to urge the Government to spend money on research in support of beneficial results but are reluctant to acknowledge that the Government would have a right to refuse to spend such public money if there is a suspicion that some potential harm might ensue. His view was that there is no doubt that the Government has the constitutional power, even the duty, to use its funding power to support or not support scientific research dependent upon a determination as to whether the research is harmless or harmful. The distinction between Government-funded research and privately funded research is, of course, crucial, since different legal principles may be involved.

D. Ethical Issues of Concern

As scientists have acquired the ability to probe into the core of life itself, broader ethical questions and their impact on science policy have been receiving special attention. Indeed, the study of ethical issues has

crystallized within the past decade to the point where several institutes now devote full time to such problems. These groups in turn have served as central resources for scholars and other institutions which have begun to examine theories regarding the role of ethics in public policy.

The DNA recombinant molecule research issue seems to be as much a struggle for the formalization of procedures for gaining broad public participation in policy determination as it is a matter of specific concern about public health and safety issues. Indeed, part of the difficulty of evaluating the policy implications of the recombinant DNA issue has been the task of identifying the concerns of specific relevance to this area of research as contrasted with the broader problems applicable to all research. As an example, almost all of the witnesses, at some time or another during their testimony revealed the value judgments about scientific research which were influencing their positions on the DNA issue even though many of the discussions were intended to focus upon scientific evidence and not ethical values. None the less, the Subcommittee did select a number of individuals known to be concentrating on the ethical aspects of public policy determination for that reason.

Dr. Lappé

Dr. Marc Lappé, Chief, Office of Health, Law, and Values, State of California, and formerly an associate of the Institute of Society, Ethics, and the Life Sciences (Hastings-on-Hudson, New York) has been studying the problem of linking scientific findings to social policy for a number of years. As he noted in his opening remarks, science remains a solitary activity while ethics is social. Dr. Lappé believes that the pressures to drive science into the arena of public activity are being countered by resistance from scientists. He cited a recent decision by the National Academy of Sciences to avoid further public involvement in examinations of the conditions for regulating DNA recombinant research. He sees an analogy between the actions of the opponents of uncontrolled "human experimentation" and the current efforts by various groups to insure a public involvement in the determination of policies for the conduct of recombinant DNA research. An important distinction which Dr. Lappé identifies in the earlier controversy over protection of individuals from dangerous experiments is the new focus on the protection of society. This places a responsibility on scientists for, as he noted in his analysis, science that is shaped by society also in turn shapes society.

Choices of areas of interest, testing methods chosen, uses to which early data are put, and other steps are conditioned by political and social perceptions of the value of the science. Since they are making decisions affecting the processes of science or the accumulation of knowledge, policymakers must consider two fundamental questions: What constraints, if any, should be imposed on science; and, second, what limits should be placed on the processes which are approved? In Dr. Lappé's opinion, both of these questions are topics warranting public scrutiny. Though he admits the dangers of potential inhibition of basic research from ill-considered regulation, he sees a logical argument for public responsibility to determine the need for public regulation. His answer to the task of evaluating science in public is to insist on involving and educating the public how and when to deny or delay the continuation of any research which compromises human

values. However, in adopting a more active role in science policy determinations, responsible public groups, such as the Congress, must examine the scientific data with a much broader set of criteria than simply the evaluation of the reliability of the experimental data. The scientific method provides for the testing of data from experiments. Policy determinations must be based on different evaluations. Issues such as who decides; what are the effects on other lines of inquiry; what is the meaning to society of the continuation of a particular line of inquiry, and similar factors are more appropriate to policy determinations. Thus scientific data alone cannot be the sole criterion for policy determinations, and representatives of the people may be justified in making a determination that human values may supercede scientific imperatives.

Professor Grobstein

Clifford Grobstein, Professor of Biological Science and Public Policy, University of California, San Diego indicated that it was necessary for legislators to be cautious with proposals for "quick-fix" legislation. Using the DNA recombinant molecule controversy as an example, he pointed out that as the research has evolved there have been changes in the perceptions of risk. Furthermore, there is an inherent difficulty in determining the future requirements for surveillance and regulation. These rapid changes in evaluations already have suggested that original proposals for legislation may have been excessive.

With this history as a brief background, Dr. Grobstein suggested that another appropriate question might be to ask whether there is enough information available to formulate sound public policy on this issue. Dr. Grobstein considers that society is in a critical period in the changing relationships between the knowledge generating body of society (the scientists) and society itself. While he considers it reasonable for society to monitor the steps being taken at new frontiers of knowledge, care must be exercised that this monitoring does not degenerate into a fear so strong that the accumulation of knowledge is threatened or extinguished. While he offers no general answer to the task at which society must work in balancing risks against benefits and freedom of inquiry against social control, the task can be simplified by classifying the research in question as to its potential consequences. The search for knowledge, in his words, requires informed consent from those who will be affected during this search. Obvious dangers need to be controlled. Longer term or less obvious potential effects require more care in evaluation. Where consequences are entirely speculative, then the burden of proof should rest on the speculator. In no instance should the freedom of inquiry be surrendered without evaluation of all of the consequences.

Although he could offer no specific formula for the solution of the need to couple the accumulation of knowledge with social purpose, Dr. Grobstein offered several suggestions. He supports the concepts offered by others that there is a need for a new forum for policy discourse. There is a need to correlate the knowledge-acquisition system to public policy formulation so that the evolution of knowledge does not surprise those with the responsibility to make the policy decisions. The DNA issue has served to focus public attention on these basic research policy issues and offers the opportunity to continue to explore new avenues for decision-making.

Professor King

Another witness supported Dr. Grobstein's concern that society may overreact to potential harm which may be associated with a particular field of research. Patricia King, Associate Professor of Law, Georgetown University Law Center, suggests that the fear by researchers of excessive control might better be countered by proceeding cautiously but in a timely fashion to newer and more effective means of control rather than reaching for total prohibition. Since the advancement of knowledge has always been held in high esteem in our society, categorical prohibitions might seriously affect the status which science has achieved. Such prohibitions might be even more harmful if they served to force researchers who defied the prohibitions to continue their work out of sight of the public scrutiny. Professor King suggests that an appropriate cost-benefit analysis offers an alternative to categorical prohibitions. She acknowledged that it is frequently difficult to collect the data which satisfies normative demands for satisfactory analyses of this type but suggests also that, as a matter of policy, the burden of proof should be on those who oppose the research where the available data are not adequate to complete an analysis. She pointed out, however, that the cost-benefit analysis should not be totally dependent upon the availability of scientific data but should also include value judgments which are necessary to such an analysis and which informed members of the society could address. If such procedures are used, there is a need for "ethical scientists" to direct attention to issues requiring evaluation. Once these issues are brought to the public attention there may be no single process for completing the evaluation.

As examples of experimental structures which have evolved to complete this process of social consideration of public policy issues, Professor King cited the experiences of the National Commission for the Protection of Human Subjects and the Joint Commission on Prescription Drug Use. Any decision reached by such bodies should be articulated in such a fashion that all interested segments of society can, in turn, be made aware of the factors which influenced the decision that was reached by the evaluating body. Both majority and minority views, or other conflicting opinions, should be clearly enunciated together with citations to related data so that a full and complete transcript of the policy determining factors may be opened to public scrutiny. There is a need, she feels, to continue the process of experimenting with methods of resolving significant scientific issues.

Professor Kass

Leon Kass, Henry R. Luce Professor, University of Chicago, cited a number of issues in biomedical research which he believes illustrate the larger scope of the problem of determining science policy. Dr. Kass considers himself a moderate in his perspective of the debates which have occurred in that he respects the scientist and appreciates the benefits of technology, while at the same time is aware of some of the costs which society has and will bear as a result of instances of misdirected technology. He enunciated a problem implied in other testimony that it is not possible to draw a clear line between good and bad research and technology. His concern extended even further, for he indicated that he perceives no clear method for deciding what should and should not be done by researchers.

In the most simple terms, Dr. Kass suggests that in areas where there is no clear cut line for decisionmaking, the best approach is to be "sensible." Attempts at regulation could be taken at the wrong time, in the wrong way, and for the wrong reasons. In reaction to speculations of potential hazard, it may be just as easy for opponents of research to do as much harm to society as has been speculated for the research in question. There is a need to determine carefully what is possible as contrasted with what is likely in making policy determinations. He is wary of attempts to limit research in the absence of careful examination of the social and ethical questions relevant to the field of research under evaluation. Since knowledge is power, there may be a need, at some time, to place constraints on the acquisition of certain kinds of knowledge if society does not have the capacity to control the power which such knowledge might provide. Such determinations cannot be made casually in a free society, however, and will require continuous consideration. It is in this area—determining the point at which inquiry and action may lead to uncontrollable or undesirable powers—that the need for careful policy determination becomes crucial.

Professor Sorenson

James Sorenson, Associate Professor of Sociomedical Science and Community Medicine, Boston University Medical School, continued a theme already advanced by noting that science and society are "beginning to alter their existing contract." This changing contract is forcing science and society to reexamine both social values and research priorities. The dialogue necessary to resolve such issues is both political and scientific.

Dr. Sorenson chose to consider both the adequacy of the current mechanisms of self-regulation of scientific research as it functions to protect society from possible dangers of research, as well as attempts to preserve social values; and, secondly, to outline a rationale as to why additional monitoring or regulation of research may be useful as well as ethical.

He cited the argument that scientists can regulate themselves and that an externally imposed formal regulation would be an abridgement of the right of the scientist to freedom of inquiry. Those who do not accept this position argue that it is impractical to ask any group with self interests to regulate itself since the values of the research group may different from the objectives of the public.

Dr. Sorenson noted that it is important to add to the record the fact that self-regulation is not absolute. The scientific community has a powerful system in place for peer review, there is public funding which must be justified and which results in public examination of proposed research areas, and members of a research team have the freedom to take issue with research programs and to take their objections to their representatives in Government. Nevertheless, failures may be expected.

Should Science Judge?

With regard to the right of freedom to inquire, society generally has assumed the role that knowledge is better than ignorance. However, Dr. Sorenson avers, there is an increasingly vocal disagreement with the concept that science should be free to make all judgments neces-

sary to complete a risk-assessment when the potential benefits or dangers from a particular type of research are being examined. It is on this aspect of scientific freedom particularly that proponents of public inquiry into the status of basic research feel that scientists have no basic right to unrestricted freedom. The argument is that since the potential for risks or benefits will affect all of society, there should be free inquiry into such analyses with all segments of society participating in the policy decisions. Those affected should have a right to express their views before research proceeds. He constructed an analogy similar to Dr. Lappé's that since research more frequently will affect society than the individual, it is as ethically requisite for society to be informed of risks or benefits as it is for the individual involved in an experiment to acquire informed consent before exposure. The decision to take a risk is not entirely a scientific question and thus cannot be resolved within the scientific community alone.

Dr. Sorenson cautions that this new perception of the right of society to a more comprehensive involvement in evaluation of research carries with it the responsibility of society to become informed about the research which is being subjected to policy evaluation. Thus, society also has an ethical responsibility. There are costs associated with this approach. It may slow research progress, monetary costs of research may increase, and of course, the possibility always exists that policy errors may still occur.

Dr. Sorenson indicated that a number of mechanisms are already present by which society can expand its participation in the evaluation of research directions and priorities. These include the hearings conducted by the various levels of Government, the professional societies, the National Academy of Sciences, and other institutions (with the implication that public interest groups are a part of these forums).

Despite the frequently dramatic citations which suggest an increasing polarization between social and scientific views, Dr. Sorenson believes that the problem may be one of public fear of disenfranchisement rather than disenchantment or disinterest with science. He views this public concern as one which can be resolved if opportunities are provided for full negotiation and bargaining between science and society. Although science is important, it is even more important for our society to maintain the right of individuals in our society to control their own destiny.

Professor Glass

H. Bentley Glass, Emeritus Professor of Biology, State University of New York, Stony Brook, and Chairman, American Association for the Advancement of Science Committee on Scientific Freedom and Responsibility, indicated his pleasure that the objectives of the Subcommittee were not limited to the public controversy over DNA recombinant research but included the broader basic ethical issues in science. He agreed completely with the view expressed by Dr. Sorenson that the historical perspective of science by society had been one of trust and a strong belief in scientific freedom as an absolute value. However, in his summary of the evolving role of science, he laid the background for his observation that today it is not enough for the scientist to have freedom, the scientist must also accept his role as a responsible member of society. The application of knowledge acquired

through research is a responsibility of scientists. He views the actions of the scientists who publicly announced the possible hazards of DNA recombinant research as a historic moment in science for to him it represents major evidence of the assumption of social responsibility by scientists. But this action did not end the responsibility of scientists to continue to participate in the evaluations of their warning. He indicated that education to develop the ability to evaluate such issues is a correlated responsibility of the scientists so that public participation may be both informed and meaningful.

Dr. Thomas

Lewis Thomas, President, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, supports the view that there is justification for legislation to regulate the introduction of new technologies based on science. Beyond this, however, he stated that the issue of regulation of science is another matter. The uncertainties as to the eventual application of knowledge which evolves from basic research makes it difficult if not impossible for society or scientists to ascertain which research should be regulated and which should not. He believes that there needs to be a careful distinction drawn between basic and applied research: in the latter field, there is frequently a much higher degree of certainty about application and thus society is in a better position to evaluate the risks and benefits.

Dr. Thomas noted that basic researchers have developed a sharp, intense method of inquiry. The good scientist knows that he will fail to secure answers to most of his inquiries. For this reason, society should be careful in any considerations which might lead to interference with this process and a concomitant inhibition of the freedom of inquiry. Once regulation of the lines of inquiry which science is permitted to follow is initiated, there may be no end to restriction of this freedom. What is needed at this stage of the social examination of freedom of scientific inquiry is a clear definition of terms. Regulation of new technologies is an entirely feasible undertaking for the law. Such regulations should focus precisely on the issue at hand. If such regulations are not carefully written, there will eventually be restraints on basic research and this could mean the loss of science. In basic research, it is impossible to predict what will be discovered. Since that is the essence of science, regulation of basic research would be arbitrary rather than balanced and could only lead to the eventual elimination of the incentive for free inquiry.

Dr. Ryan

Kenneth J. Ryan, Chairman of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and Professor of Obstetrics and Gynecology, Harvard Medical School, commented on the problems of gaining public participation in evaluation of scientific research. He noted that while the subcommittee's objective included an examination of the ethical methods for examining public policy issues, Committee Members should be aware that there is no single system of ethics in our society. Even ethicists argue about what constitutes an ethical principle. While ethicists may help in constructing principles for examination, this does not in turn make an ethicist more qualified to apply such principles to a particular problem. As an example, the evaluation of the benefits to society which have

been postulated as an expected product from successful application of the DNA recombinant technique is, in fact, a value judgment. Such value judgments differ among individuals with different expectations and experiences. The role of public policy groups should be to provide an opportunity for acquiring a cross section of these value judgments so that a consensus may be obtained. Thus, Dr. Ryan believes, the ethical dimensions of any public policy consideration of recombinant DNA or any other similar issue should be a rational review of facts and issues at hand, an examination of principles basic to our society, and the selection of the most obvious reasonable options for the policy decision.

Dr. Ryan further explained that a central theme within our society is respect for the individual; this includes freedom of thought and freedom of inquiry. Repression of these freedoms has led to the construction of societies which this Nation currently considers unacceptable forms of government. However, the associated concept in our society that resources should be allocated equitably requires that freedom of inquiry must frequently be balanced against priorities in public policy decisions. Such balances have not been achieved in our society as yet and this is one of the sources of distrust and suspicion which produces debates similar to the current one on DNA recombinant research. As Dr. Ryan said, "Valid value judgments can be made only when sufficient factual information is available. The bitter debates and public posturing in the DNA controversy have confused the issue over what is known and what is conjecture. The likely outcome will be to proceed with caution."

E. General Views and Perspectives

As noted earlier in this summary, the authority of the Constitution, and particularly the first amendment, was examined to determine whether any inherent legal right to freedom of inquiry exists. In concluding testimony, Howard T. Markey, Chief Judge, U.S. Court of Customs and Appeals, addressed a number of issues from his experience in the judiciary.

Judge Markey

Chief Judge Markey observed that the Constitution grants no specific powers to the Congress with regard to scientific research. He added the observation that the writers of the Constitution would probably have included today the additional statement that "Congress shall make no law abridging the freedom to learn." Science in his view is another part of the learning process. He referred to technology as an application of knowledge. Thus, he was constructing the same perspective about regulation that several other witnesses had acknowledged. There is a need to examine carefully the distinction between the freedom of inquiry, or learning phase, and the responsibilities for action, in this case, the use of technologies. Chief Judge Markey summarized his views in such a way as to emphasize the extreme caution which should be taken before any infrigement on the freedom of inquiry is initiated, while at the same time he readily acknowledged the right to regulate following due process examination and determination of the need to regulate. The problem then becomes one of determining whether regulation can be constructed in such a way as to

avoid infrigement of the right to learn while providing the protection to society determined to be necessary before approving or limiting the application of a technology. The duty of the Congress, and other concerned groups, may be one of remaining informed so that the time for action and the type of action required may be determined. Chief Judge Markey emphasized the need for continual improvement of communication channels between science and society, not only in terms of awareness but also in terms of new concepts discussed in a readily understood fashion. Scientists must learn to present their ideas in as simple a fashion as possible so that there can be no exaggeration or misconceptions about what is being discussed. This failure to comprehend fully the precise meaning of new developments often leads to exaggerated fears or expectations. Neither of these conditions is conducive to an improved public participation in consideration of science policy decisions.

Dr. Edsall

John T. Edsall, Professor of Biochemistry, Emeritus, Harvard University, identified two fears which he believes concern the critics of DNA recombinant research. One, the fear of producing new pathogenic organisms and increasing the incidence of disease; and second, the fear that the knowledge we attain may be more than we can wisely use.

With regard to the first fear, Dr. Edsall expressed his opinion that the approaches being taken within the NIH guidelines seem rational and well defined to produce as low a probability of occurrence of any untoward event associated with the first fear. Total prohibition would probably be an unacceptable restriction of freedom of inquiry and is the next step which would have to be taken if the guidelines are not acceptable. An evaluation of the second fear is more complex. Dr. Edsall suggested that we may have to take our chances that research may occasionally produce potentials for misapplication with which we will have to cope. He shares Dr. Thomas' views that we are really profoundly ignorant of the fundamentals of biology. He believes that deeper knowledge will be accompanied by deeper wisdom. The only way that we can assure ourselves protection from the second fear would be to abolish scientific research entirely, and he considers this alternative unacceptable in our society.

Dr. Sonneborn

Tracy Sonneborn, Professor Emeritus of Biology, Indiana University, humorously observed that one of the disadvantages of being a late witness is that everything which needs to be said has been said. He noted that several of the preceding speakers had made the same points with which he had been concerned. He agrees that the need for education on evolving scientific developments for the public, and on social responsibility for the scientists, continues to be an important task for all. He shares the view that there is a need for an expansion and improvement in the mechanisms for public involvement in matters pertinent to science policy determinations. He urges increased communication of ideas, internationally as well as domestically between science and society. The specific issue which was the theme of these hearings, DNA recombinant research, is not limited by national borders and thus must be addressed within the international forums available.

Dr. Sonneborn emphasized that care must be taken in the promulgation of regulations. As noted by other panelists, even though a scientist may complain about the restrictions on certain kinds of research, if these restrictions are reasonable, and flexible enough to be modified quickly when new data permit, the vast majority of scientists would rather work amicably within this framework than be placed in the undesirable position of constantly defending their work. Scientists are citizens as well as scientists, and the respect of their social peers is important as is the respect of their professional peers.

Dr. Sonneborn concluded that basic research is an extremely demanding occupation. The environment for such work must provide an opportunity for creative and original thought. Restrictive regulation which attempts to anticipate every conceivable risk would reduce this environment to an undesirably tense situation, create anxiety, and interfere with the serenity necessary for such work. If our society wishes to continue to flourish in an atmosphere of freedom, care must be taken to limit the restrictions imposed on scientists, as well as those imposed upon all citizens.

APPENDIX

[From the Washington Post, Dec. 17, 1977]

Discoverer Would Lift Curbs on DNA

(By Victor Cohn)

Dr. James Watson, the Nobel Prize-winning co-discoverer of the structure of DNA, the stuff of genes, surprised colleagues yesterday by calling for an end to government restrictions on DNA research as unneeded "nonsense."

He said "there is no evidence" that experiments in recombining DNA can do anyone any harm, the time and dollars wasted on maintaining restrictions is "enormous," and he and other scientists who recommended the precautions in the first place were "stupidly" wrong.

The emotional plea from the slender, intense Watson—who three years ago just as emotionally called for the restrictions—sent a shockwave through a National Institutes of Health advistory committee weighing changes in the restrictions.

But it did not make any of the advisers recommend abandoning them entirely without more evidence that some of the original fears of Watson and other scientists can be forgotten.

The advisers, in fact, ended a two-day public hearing with a discussion in which most of them endorsed most of NIH's new plans to modify the restrictions but keep them in effect for most researchers.

"Watson has put some questions in our mind that I think we need to consider very carefully," but "I don't think he's right—he's his usual extreme," said Dr. Walter Rosenblith, provost of Massachusetts Institute of Technology.

"Jim is speaking, I think, for a large group of scientists"—that is, a probable majority who now agree with him—and much of what he says may be correct," commented Dr. Alexander Rich of MIT, co-chairman of a National Academy of Sciences forum on the DNA problem this year. But the "prudent" and "correct" course, he said, is to modify the rules only as new evidence shows the research to, be safe It was the "extreme" Watson who, as an extremely emotional and highly original young man, joined Britain's Francis Crick to first describe the double-helix-shaped molecule which is the chemical of thegenes in every organism.

Three years ago, Watson and a small group of others first warned that new experiments splitting and then "recombining" the DNA of various organisms could create new life forms having unknown powers.

The precautions have become a "disaster," Watson said yesterday, and the public has been misled into fearing "madman scenarios."

Various scientists' original fears were, mainly that a cancer virus might be let loose, or other diseases or epidemics might be created, or that scientists might cause subtle but disastrous changes in the genes of even lowly animals or organisms to somehow disturb the whole earth's ecology.

The first two fears were the main ones Watson said laboratory experiences have now shown that, first of all, no one has gotten sick and, second, organisms in nature exchange DNA widely without disaster.

On a scale of things to worry about, he maintained, genetic research is "trivial." And "if you worry about changing man's genetic nature," he said, "you should worry" about regulating sex. "Maybe we should have a committee there" or require that all sex be performed at Fort Detrick," he said.

But some advisory committee members said genetic research is moving humankind toward genetic engineering, so a pause now for reflection is wise and not rash.

"God forbid" what the public would have thought if scientists themselves had not called attention to some of the dangers, said Patricia King, associate law professor at Georgetown University.

The scientific evidence on recombinant DNA's possible safety and the possible ubiquity of DNA combinations in nature is just starting to come in "and most of us haven't seen the scientific papers yet," said Dr. Robert Sinsheimer. A prominent biologist and critic of this research, he recently became chancellor to the University of California at Santa Cruz.

[From Science Magazine, Sept. 30, 1977]

Recombinant DNA: NIH Rules Broken in Insulin Gene Project

(By Nicholas Wade)

A breach of National Institutes of Health rules on gene splicing occurred earlier this year in the Department of Biochemistry and Biophysics at the University of California, San Francisco, one of the leading centers for practice of the new technique. No hazard resulted, but the episode underlines some of the difficulties experienced by research laboratories in adapting to the new rules.

The breach was the use of a biological component, or "vector," before it had been certified by the NIH director. The researchers, a team engaged in isolating the rat gene which codes for insulin, say they destroyed the experiment as soon as they realised their mistake.

The experiment was repeated in a certified vector and published in *Science* on 17 June. It received considerable attention because the researchers had achieved, much earlier than expected, the first step toward the goal of isolating the human insulin gene and using it for the manufacture of insulin protein. The UCSF team was in competition with a group at Harvard which was known to be working with a better source material.

USCF's preeminence in the gene-splicer's art has brought it some mixed blessings. Because of the practical implications of what its researchers are doing, a company called Genentech has established a relationship with Herbert Boyer, one of the pioneers of the technique. Members of the insulin team have set up a nonprofit corporation, the California Institute for Genetic Research. These commercial developments are a tribute to the department's success, but have also created internal stresses. "Capitalism sticking its nose into the lab has tainted interpersonal relations—there are a numbr of people who feel rather strongly that there should be no commercialization of human insulin," says UCSF microbiologist David Martin.

Another mixed blessing is fame, which has attracted press attention not only to the department's achievements but also to certain internal tensions. A lengthy and circumstantial article in the June issue of the *Smithsonian* called into question the respect accorded to the NIH safety rules by UCSF researchers, and in particular by the younger, postdoctoral workers who perform most of the experiments. Written after a 3-month internship in Boyer's lab by Janet L. Hopson, formerly a reporter for *Science News*, the article observed that "half of the researchers here follow the guidelines fastidiously; others seem to care little. . . . Among the young graduate students and postdoctorates it seemed almost chic not to know the NIH rules," Hopson noted. In a letter to the editor criticizing the article, Boyer stated that "In practice [the NIH rules] are followed seriously."

The stresses of both commercial success and media attention came together this May when the insulin team announced their production of the rat gene.

Other researchers resented not only the intrusive presence of the press but also the fact that they were hearing of their colleagues' success for the first time. The team had worked in unusual secrecy, which many regarded as inappropriate in an academic setting as well as disruptive. "People would stop talking when you came into the room, or change the subject if you tried to make conversation about how the insulin project was going," says UCSF biochemist Brian McCarthy. The insulin team say that no secrecy was intended, and that it was the speed of obtaining results that occasioned surprise.

The secrecy and suspicion surrounding the insulin gene experiment, together with perhaps a touch of resentment, helped to fan rumors within the department alleging that the NIH rules had been broken and even that the experiment published in *Science* might not have been performed as described. The focus of the rumors was the obvious fact that the whole intricate experiment had been completed only 3 weeks after the NIH had certified the vector which the researchers used. Even experienced gene splicers were surprised by the rapidity of execution. "It is conceivably possible to do such an experiment in three weeks if everything works perfectly the first time, but you know as well as I do that science never works as well as you hope," a member of the department remarks.

"Well, what can I say? It did work well. We were all set to go," says a member of the insulin team queried on the speed of the experiment. Yet members of the team concede that an earlier experiment took place, but say it was aborted half way through and before any pertinent information had been gained.

The episode of the earlier experiment illustrates the problems experienced by research laboratories both in acclimatising to the NIH's gene-splicing rules and in devising ways of enforcing them. "We can't run a policing service," says David

Martin, until recently the chairman of the UCSF biosafety committee. "What we do is to try to raise the consciousness of the individuals involved to make them respect the guidelines." Martin spent 2 days investigating the episode and concluded that a breakdown in communications was responsible. Precise details remain obscure because the minutes of the biosafety committee record only Martin's conclusion, and a lengthier account prepared for the minutes by the present chairman, James Cleaver, is far from complete.

The episode revolves about the use of the vectors—virus-like entities known as plasmids—which are used to carry genes of experimental interest into bacterial hosts. Two particularly useful plasmid vectors, known as pBR322 and pMB9, had been developed by Boyer and others. But before either could be used, it had to go through a two-stage administrative process, the first of being approved by the NIH recombinant DNA committee and the second of being certified by the NIH director. Vectors, in other words, are off limits to researchers until certified.

Plasmid pBR322 was tentatively approved by the NIH committee on 15 January, finally approved on 23 June, and certified for use on 7 July. Plasmid pMB9 was certified on 18 April.

According to both Martin and two members of the insulin team, the episode of the earlier experiment was as follows. Early this year, sometime in February, an attempt was made to produce copies of the rat insulin gene with pBR322 as the vector. The gene was linked to pBR322 and the plasmids inserted into NIH-certified bacteria designated EK2 hosts. Some of the bacteria were successfully colonized by the plasmids. To verify that clones of colonized bacteria contained the rat insulin gene it would have been necessary to carry the experiment to completion by extracting and analyzing the DNA sequence of the genes. This step was not performed because at that moment, on or around 1 March, the team say they learned that the plasmid had not been certified for use. They decided to destroy all their clones. Further attempts were made to clone the gene with an already certified vector, known as pCR1, but without success.

When pMB9 was certified, team members say, they had all their materials ready to go, and repeated the experiment from scratch in the new plasmid. Martin says that he inspected the team's records and has "complete confidence" in their statement that the entire experiment was done after the approval of pMB9. "When the manuscript appeared so soon, people said 'How in hell can you do it?' But you can do it—the experiment was very straightforward," Martin said from Great Milton near Oxford, England, where he is at present on sabbatical. "I think they realized they would be questioned and that if there were any shenanigans they would be really jeopardizing a hell of a lot, not only their own careers but the whole advance of science through recombinant DNA technology."

In the categories of the NIH rules, the experiment with pBR322 was assigned to the highest available containment level short of going off campus to a specially secure laboratory. But it is clear that the experiment posed no issue of public health since it was performed in the required type of laboratory—a "P3" facility—and with a vector which has now been certified as safe.

The experiment also took place at a time when the NIH rules were still new and local procedures for implementing them were still in a formative stage. "This was one of the inevitable things that happened as we tried to evolve a new system," comments biosafety committee chairman Cleaver.

Not wholly plain from the Martin-Cleaver accounts of the episode is how the insulin team came to believe it was all right to go ahead with pBR322 prior to certification. Howard Goodman, chief of the laboratory which did the cloning and sequencing part of the experiment, is out of the country, as he has been for most of the past year. One of his postdoctoral colleagues says there was great confusion at the time about the status of the plasmid but the reason for the confusion is "sort of cloudy now."

According to Martin, it was clear that everyone knew that pBR322 had been approved but not certified, but the NIH, Martin says, was advising researchers that certification was imminent and that they should go ahead. According to the minutes of the 20 May meeting of the UCSF biosafety committee, Martin reported that the researchers "had been verbally informed that the certification of an approved EK2 vector was imminent and to proceed with its use."

This version is strenuously denied by William Gartland, director of the NIH Office of Recombinant DNA Activities, and by his only assistant, Daphne Kamely. Both say that they would never have advised use of any vector before certification. Gartland notes that the team "must have got the vectors from Boyer, who certainly knew they were not certified" because Boyer had complained repeatedly

to the NIH of the delay in certification. According to Boyer, the insulin team "kept on asking" if the plasmid had been certified and he told them it had not. Boyer states that he never encouraged anyone to go ahead prior to certification. Thus the source of encouragement for the team to go ahead prior to certification remains obscure.

A different account from Martin's is given by William Rutter, a member of the insulin team and chairman of the UCSF Department of Biochemistry and Biophysics. In its memorandum filed with the UCSF biosafety committee, the insulin team had said it would use as vectors pCR1 and any other vectors that might in future be approved by the NIH recombinant DNA committee. When the NIH committee approved pBR322 on 15 January, Rutter says—(the committee gave tentative approval on 15 January and full approval on 23 June)—he therefore assumed that pBR322 was sanctioned for use, since he was not then aware of the NIH distinction between approval and certification.

The UCSF biosafety committee did not learn until May that the pBR322 experiment had taken place. Researchers doing recombinant DNA experiments are required to file a description of the experiment for committee approval. But, as Rutter has said, the memorandum filed by the insulin team did not mention pBR322 specifically. Researchers using the P3 laboratory at UCSF are also required to sign a logbook describing their experiment. Yet Martin says that when he inspected the logbook at the outset of his investigation, he found "nothing recorded." Those in charge of the facility "were not being compulsive enough in seeing that people were filling in the logbook"—a situation which has now been corrected, Martin adds.

Cleaver, Martin's successor as biosafety committee chairman, told *Science* that two entries from the insulin team are recorded in the logbook between 1 February, when the logbook was instituted (the P3 lab officially opened on 9 November 1976), and the end of April. An entry on 1 February notes in the column headed "vector" that pCR1 will be used, and the second entry on 23 April gives pMB9 as the vector. The pBR322 experiment, according to Rutter, took place after 1 February. The vector was not mentioned, he says, because the 1 February entry referred to the general experiment already described in the memorandum filed with the biosafety committee, in which the team had said it would use pCR1 and other approved vectors, and the logbook has to be signed only for each experiment, not for each use of the laboratory. "The signing in of the logbook meant the insulin cloning experiments in general. The vectors were not designated specifically, and that was just human error," says Rutter. Rutter's laboratory provided the insulin gene for the experiment; it was members of Goodman's laboratory—Goodman was away until mid-April—who performed the cloning experiments.

How should a local biosafety committee respond to an incident of this sort? "I would have expected that the biohazards committee to have investigated the whole thing," says Gartland. Martin did conduct an investigation, and he took action both with the NIH and the insulin team. "I felt comfortable we had resolved the question and eliminated the possibility of it happening again," he says. But in fact, written documents of the committee record criticism only of the NIH.

The pBR322 experiment raises no question of hazard but it does raise the possibility that the insulin team might have gained an unfair advantage over other researchers who had abided by the NIH rules. Another team at Harvard is also working on the same problem. Members of the UCSF team say that they gained no information from the pBR322 experiment which was helpful to the later experiment with pMB9. As it happens, the Harvard team was not neck-and-neck with UCSF because it has not even now published any results.

As far as is known the pBR322 experiment is the only occasion on which the NIH rules governing recombinant DNA research have been broken. The researchers say that the breach was the result of innocent error, a statement not refuted by the available evidence. The experiment presented no hazard to public health nor, in the event, was any unfair advantage gained over competitors. As for the UCSF biosafety committee, its response included action to ensure against repetition of the incident, although not a full public account. The committee's discussion of the experiment, as reflected in the minutes of its 20 May meeting, is confined to an attempt—unsupported by available evidence—to ascribe the error to confusion generated by NIH. But both the experiment and the biosafety committee's response to it occurred in circumstances to which researchers were then still adapting, and for which there were few, if any, precedents.

[From the New York Times, Dec. 16, 1977]

Health Institutes' Action Prompted by Procedural Violation of Rules on Recombinant DNA Research

(By Harold M. Schmeck Jr.)

Bethesda, Md., Dec. 15—The National Institutes of Health have for the first time ordered a laboratory to halt gene-splicing research supported by a Federal grant because of a procedural violation of the rules governing such studies.

A spokesman for the agency said today that the violation did not involve any known safety rules or laboratory procedures. The action involved a laboratory at Harvard Medical School where recombinant DNA research, popularly known as gene-splicing research, has been in progress for several years. The investigation by the agency is continuing.

The agency supports with funds more than 250 projects in recombinant DNA work at 110 institutions. Such research embraces experimental techniques that have been a subject of much controversy because of the view of some critics that they are potentially dangerous and might lead to deliberate manipulation of heredity in ways the critics consider improper.

Many scientists consider the techniques extremely useful as a tool for learning more about the chemistry of genetics and possibly for developing important medicinal drugs and coping with some presently untreatable genetic diseases.

For about a year Congress has been considering legislation to set rules for all recombinant DNA research, but has not acted.

MEMORANDUM OF AGREEMENT

The specific procedural violation made known today was Harvard's failure to get an approved memorandum of understanding and agreement concerning the laboratory's experiments before the work actually began. The reason for this failure is unknown.

The violation came to light because of a Freedom of Information request from Leslie Dach of the Environmental Defense Fund, who said today that he made the inquiry because of reports that persons in the laboratory had been using poor laboratory procedures in some of the experimental work.

After his request for information on the laboratory's work, the N.I.H. investigated and found that the required agreement was lacking. Three officers of the institutes went to Boston for further investigation.

Neither he nor spokesmen for the Institutes could confirm today the reports of poor laboratory procedures. Mr. Dach disclosed the agency's action here after the opening session of a special meeting of the advisory committee to the director of the agency. The meeting was called to advise on proposed changes in the guidelines drafted by the Institutes to cover gene-splicing research by scientists working on Federal grants or contracts.

GUIDELINES OF THE AGENCY

The National Institutes of Health is the Federal Government's main agency for conduct and support of biomedical research. The agency's guidelines on gene-splicing research are considered binding on virtually all such research supported by any Federal agency. The guidelines are not yet binding on industry.

DNA, or deoxyribonucleic acid, is the active substance of genes. It is therefore the key chemical in the heredity of all life. The recombinant DNA techniques makes it possible to splice genes of widely divergent species, human and bacterial for example.

One recent set of experiments succeeded in altering the genetic imbalance of bacteria so that they produced a hormone normally produced only in animals and man.

In a letter to Harvard Medical School made public today, an officer of the Institutes said that experiments under the grant in question "must not be carried out in the absence of an approved M.U.A.," or memorandum of understanding and agreement.

The laboratory is that of Dr. Charles A. Thomas Jr., and an official of the Institutes said today that the grant was in the third of five planned years. The grant totals roughly $100,000 a year, according to agency figures, but only part of this involves recombinant DNA work.

The agency is also investigating possible violations of the recombinant DNA rules by a group at the University of California at San Francisco.

The two-day meeting that began at the Institutes here today is considering a set of proposed revisions in the guidelines first published in the summer of 1976 to govern Federal grantees involved in gene-splicing studies.

Opening today's session, Dr. Donald S. Frederickson. director of the agency, described the issue of guideline revision as "a matter of considerable national and even international interest."

RELAXING THE RULES

In some respects the proposed revisions, first made public this fall relaxed the rules, removing some experiments from coverage by the guidelines and changing safety requirements for others. The revisions have been made by a special committee established by the Institutes on the basis of data that have accumulated in recent years concerning the research.

One document made public concerning the revisions said that the guidelines continued to be deliberately restrictive with the intent of erring on the side of caution, although "everything we have learned tends to diminish our estimate of the risk" involving the major area of experiment in which the proposed revisions offer some relaxation.

Some speakers today criticized the proposed relaxations for being unjustified and criticized the procedures of revision for not including sufficient contribution from critics or allowing enough time for a study of the documents.

One invited speaker from Europe, on the other hand, said that some features of the guidelines were much too stringent. This view is held by some American scientists and contested by others.

[From the Wall Street Journal, Jan. 26, 1978]

POLITICS AND PEOPLE

(By Alan L. Otten)

PATENTING LIFE

Washington—A tiny number of government officials, lawyers and scientists have begun wrestling with a huge legal problem: Should forms of life be patented?

Ultimately, the Supreme Court or Congress may have to provide the answer. It's another area where rapidly expanding scientific knowledge is creating tricky new ethical, legal and social quandaries.

The question immediately at stake is whether patents should be granted for microorganisms, those minute living and reproducing bacteria, viruses and other organisms. In one case, an appellate court has already answered in the affirmative, and a second case is waiting decision.

Many experts believe the issue will remain narrowly focused on microorganisms in food, drug, chemical and similar products, and that the courts can be counted on to avoid any science fiction horror extensions of patentability. At least a few others, though, contend the principle affirmed by the court could easily be applied in far-out and scary directions; to patent products of recombinant DNA technology, cloning, cell fusion and other genetic engineering, perhaps organic modification of animals or even humans.

The patent law, dating back to the earliest days of the republic, authorizes patent protection for the invention or discovery of "any new and useful process, machine, manufacture or composition of matter." The idea, of course, is to encourage research and invention by guaranteeing a temporary monopoly on the product. A 1930 law extended coverage to certain "asexually reproduced" new plant varieties.

It's long been assumed that the processes for producing a particular microorganism and the methods for using it could be patented, but the question of patenting the organism itself—without doubt, a form of life—hadn't been seriously addressed until recently. Then Upjohn Co. sought a patent for a microorganism it had isolated from a soil sample and produced in a biologically pure culture, useful for preparing the antibiotic lincomycin.

A government patent examiner ruled the microorganism a "product of nature" and therefore not entitled to patent protection. A three-man appeals board within the Patent and Trademark Office also refused the patent, by a two-to-one vote, but the majority gave a different reason: A microorganism is "a living organism" and Congress never meant living things to be patentable.

Upjohn appealed to the Court of Customs and Patent Appeals, and a three-to-two vote last fall overturned the board and authorized granting the patent. The majority, which included a judge from another appellate court sitting in for an

ailing regular member, insisted its ruling was very limited. "We are not deciding," it said, "whether living things in general, or, at most, whether any living things other than microorganisms, are within (the patent law). These questions must be decided on a case-by-case basis."

Nonetheless, other statements seemed quite broad. The majority flatly declared that the fact that the culture was "alive" did not remove it from patent protection. In fact, it added, it is precisely "because it is alive that it is useful." The judges said that microorganisms, like inanimate chemical compounds, were essentially manufacturing "tools," and declared that "the fact that microorganisms, as distinguished from chemical compounds, are alive is a distinction without legal significance."

The minority judges, including a former U.S. Senator, maintained that "the nature of organisms, whether microorganisms, plants or other living things, is fundamentally different from inanimate chemical compositions." Moreover, they said, there was no reason to believe that any legal distinction could be drawn "between microorganisms and more complex living things." The whole subject, they argued, should be left for Congress to determine.

The Government has about a month left to decide whether to appeal this decision to the Supreme Court. Meanwhile, another application is raising the issue in a somewhat broader form, one that even attorneys who support the court's Upjohn ruling concede moves a significant step closer towards recombinant DNA technology.

In this case, General Electric Co. is seeking a patent for a bacteria that contains extra-chromosomal genetic material that produce soil-degrading enzymes—a discovery of obvious use in combating oil spills. A different patent examiner and a different three-man PTO appeals board have unanimously turned down the application, and GE has appealed to the Patent Appeals Court. Argument was heard in December—with the previously ill judge back on the bench—and the court hasn't yet made its ruling.

Ever since the Upjohn case started making waves, there's been intense discussion in legal circles. Several attorneys think that, as Wisconsin law professor John Stedman puts it, "the courts will find a way to keep things within bounds," without any need for Congress to step in. Says patent attorney Donald Dunner: "As soon as you discuss patenting living organisms, people have visions of 1983. But I think it's raising more passion than perhaps necessary."

Other students, though, reject the relaxed view. "I'm not sure the court's ruling is quite as limited as it says," asserts one corporate attorney. "It raises the question of whether ultimately someone could patent a human being—and that should be up to Congress, not to a couple of judges."

PTO Associate Solicitor Gerald Bjorge stated this view in only half-facetious terms during oral argument in the GE case. "My children's Shetland sheepdog," he said, "was new and useful when it came into the world. We feed and culture it, and it is our burglar alarm. My childen's cat was new and useful and we feed and culture it, and it is our mousetrap. How does this court ever hope to distinguish between one living organism and another? Where and how will it draw the line?"

[From Business Week. Dec. 12, 1977]

A Commercial Debut for DNA Technology

A tiny San Francisco company, just two years old, has scored a biomedical research coup that may have left its competitors in the dust. Genentech Inc. will get the patent rights to a new means of producing a brain hormone called somatostatin. But the exciting news is that scientists for the first time have employed controversial recombinant-DNA (gene-splicing) technology and the young science of artificial gene synthesis to produce the hormone. In addition, somatostatin has potential both as a research tool and as a medicine, and variations on its structure might well open the way for a whole new family of drugs capable of treating diseases that today defy medicine's best efforts.

The scientific breakthrough came at the University of California at San Francisco, where researchers—along with the City of Hope Medical Center in Duarte, Calif., and the Salk Institute—had been pursuing the new technique since mid-1976. "Molecular biology has reached the point where it can become involved in industrial applications," says Herbert W. Boyer, leader of the research team and a co-founder of Genentech, who now serves as a consultant to the company. "Our strategy," says Robert A. Swanson, Genentech's 30-year-old president, "is to concentrate solely on recombinant DNA and to manufacture and market products to major medical, pharmaceutical, and industrial companies."

Lots of competition.—Genentech's connection with UC-San Francisco has led to unease among scientists in Boyer's lab—a feeling that is shared by some science policy advisers within the White House. And the advance comes at a time when many scientists and citizens still worry about recombinant-DNA research and its potential for harm.

Nevertheless, there are nearly 300 recombinant-DNA research programs now under way in the U.S., most of them funded by the National Institutes of Health (NIH), which oversee the safety of such experiments. Though Genentech followed NIH guidelines, because of the unique arrangement covering its research, the company will be first to exploit the somatostatin results commercially. Once production is under way—perhaps by the middle of next year—UC-San Francisco will share in the royalties, along with the City of Hope where the gene synthesis work was done.

Funding such research is expensive: The somatostatin experiments alone cost several hundred thousand dollars. But Swanson claims to have raised nearly $1 million in backing so far from sources such as International Nickel Co. and his former employer, the venture capital firm of Kleiner & Perkins. Despite the obvious risks of exploiting an unproven technology, Swanson insists that "our investors have deep pockets."

Though Genentech seems to have a clear headstart, it is by no means alone in its determination to cash in on the potential of recombinant-DNA technology. Across the bay in Berkeley, six-year-old Cetus Corp. is also opening a recombinant-DNA facility to complement its work on conventional chemical and radiological means of mutating bacteria. "This is the hottest area in biology today," says Peter J. Farley, Cetus' executive vice-president. Two months ago, Standard Oil Co. (Indiana) bought one-fifth of Cetus for about $10 million.

Elsewhere, Upjohn Co. will soon open its own recombinant-DNA lab. According to Joseph E. Grady, head of Upjohn's infectious disease research, the company expects to develop marketable applications within five years. Abbott Laboratories is just now beginning work on recombinant DNA, while Miles Laboratories Inc. is becoming the major supplier of the so-called restriction enzymes that scientists use to cut strands of DNA for recombination. Altogether, between 10 and 15 industrial labs are now pursuing recombinant-DNA experiments.

Trying for insulin.—The Genentech research began with the construction of an artificial gene by the team at the City of Hope under the leadership of molecular biologist Arthur D. Riggs. The scientists chose to construct the gene for somatostatin because the hormone's chemistry, worked out at the Salk Institute, is reasonably well-known, and because sensitive tests are available to measure whether it is actively working within a cell. More important, somatostatin seems to play an important role in regulating body growth and inhibiting the production of insulin in the pancreas. Thus, it and other hormones now under study seem to have wide possible application in treating diseases such as diabetes. Today, somatostatin costs around $30,000 per gram to synthesize chemically, but Genentech believes it can bring the cost down to $300 or less.

Once it had an artificial gene, Boyer's team at UC-San Francisco used restriction enzymes to cut open a ring of DNA known as a plasmid in the cells of a special strain of *Escherichia coli*, the human gut bacteria most commonly used in recombinant-DNA work.

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95TH CONGRESS } HOUSE OF REPRESENTATIVES { REPORT No.
2d Session } { 95-1005, Part 1

RECOMBINANT DNA ACT

REPORT

BY THE

COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE

together with

DISSENTING AND SEPARATE VIEWS AND INCLUDING THE CONGRESSIONAL BUDGET OFFICE COST ESTIMATE

[To accompany H.R. 11192]

MARCH 24, 1978.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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95TH CONGRESS } HOUSE OF REPRESENTATIVES { REPT. 95–
2d Session } { 1005 Part 1

RECOMBINANT DNA ACT

MARCH 24, 1978.—Ordered to be printed

Mr. STAGGERS, from the Committee on Interstate and Foreign Commerce, submitted the following

REPORT

together with

DISSENTING AND SEPARATE VIEWS

[To accompany H.R. 11192]

[Including the Congressional Budget Office cost estimate]

The Committee on Interstate and Foreign Commerce, to whom was referred the bill (H.R. 11192) to extend for 2 years the scope of the containment requirements and the requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation, having considered the same, report favorably thereon with amendments and recommend that the bill as amended do pass.

The amendments (stated in terms of the page and line numbers of the introduced billl) are as follows:

Page 3, beginning in line 11, strike out "have been formed by joining together DNA segments in a cell free system" and insert in lieu thereof "are formed by joining together DNA segments outside of living cells".

Page 5, line 18, insert "tenth day after the" before "date of".

Page 5, beginning in line 22, strike out "ninety days from the date of the enactment of this Act" and insert in lieu thereof "ten days from the date such regulations first take effect under such subsection".

Page 6, line 10, insert ", in accordance with regulations promulgated under subsection (d)," before "such".

Page 7, strike out lines 7 through 9.

Page 7, strike out "Act" in lines 21 and 22 and insert in lieu thereof "title".

Page 11, line 17, strike out "(E)" and insert in lieu thereof "(B)".

Page 11, beginning in line 19, strike out ", facilities, and alll other things in the place" and insert in lieu thereof "and facilities".

Page 15, insert after line 17 the following:

RELATIONSHIP TO OTHER FEDERAL LAWS

SEC. 108. (a) Ths title shall not affect the authority of any Executive agency (as that term is defined in section 105 of title 5, United States Code) to regulate under any other Act recombinant DNA activities.

(b) In exercising any authority under this title, the Secretary, or any person acting on behalf of the Secretary or pursuant to this title, shall not, for purposes of section 4(b)(1) of the Occupational Safety and Health Act of 1970, be deemed to be exercising statutory authority to prescribe or enforce standards or regulations affecting occupational safety and health.

Page 19, line 16, strike out "(a)" and insert in lieu thereof "(b)".

PURPOSE OF LEGISLATION

The purpose of the legislation is to assure that all research and other activities involving recombinant DNA molecules are conducted in accordance with national safety standards designed to prevent the creation and escape of genetically modified organisms or viruses which could pose a threat to public health or the environment. At the same time, however, the use of recombinant DNA methods is recognized to be of exceptional value to science. Thus, an additional purpose of the legislation is to prevent the imposition of unnecessarily restrictive state and local requirements.

At present, work in this area supported or conducted by the National Institutes of Health must be carried out in accordance with safety guidelines prepared and released by NIH. Most other Federal agencies have adopted the NIH Guidelines as agency policy. However, some public and all private recombinant DNA activities are not bound to follow any set of safety precautions.

H.R. 11192 is a 2-year interim control bill which would:

(1) Require that the sections of the NIH Guidelines, as currently amended, on Containment (Section II) and Experimental Guidelines (Section III) apply to all parties conducting recombinant DNA activities;

(2) Empower the Secretary of Health, Education and Welfare to promulgate administrative regulations, revise the Guidelines to reflect new scientific data, and exempt from the Guidelines activities determined to present no significant risk to health or the environment or for specific risk assessment studies;

(3) Give inspection authority to the Secretary of HEW and empower him to enforce the Guidelines, as appropriate, by (a) suspension of research grant funds, (b) a civil penalty ($5,000) or (c) seeking an injunction through the courts;

(4) Preempt States or political subdivisions thereof from establishing or continuing in effect any requirement for the regulation of recombinant DNA activities. However, the Secretary would be authorized, upon application and after considering local conditions, to approve a State or local requirement if it is the same as, or more stringent than a Federal requirement and if the additional requirement is necessary to protect health or the environment; and

(5) Establishes a study commission to evaluate Federal policy on activities involving genetic manipulation as well as the long term applications of gene splicing technology.

The interim controls and the study commission are established for 2 years. The Committee anticipates that within 1 to 1½ years after enactment, the appropriate Congressional subcommittees would exercise their oversight responsibilities to assess the current need for uniform standards and the performance of DHEW in administering the NIH standards to all parties. Based upon the performance of the Department and the current state of the art, appropriate legislation will be developed as needed.

SUMMARY OF THE LEGISLATION

Scope of legislation

The safety standards cited in this act, as well as any administrative requirements or regulations promulgated by the Secretary, would cover any activities (including research, transportation or commercial activities) involving recombinant DNA molecules which are addressed in section III of the NIH Guidelines, unless specifically exempted under this act. They would, therefore, apply to all private and governmental entities engaged in such activities.

Only activities involving recombinant DNA molecules which are formed by joining DNA segments outside of living cells are included in Title I of this Act, which establishes interim regulation of recombinant DNA activities. However, the scope of the study commission as set forth in title II, includes all types of genetic manipulation.

This act expires 2 years from the date of enactment.

Administrative responsibility

The responsibility for implementing the Recombinant DNA Act would rest entirely with the Secretary of Health, Education, and Welfare. However, the legislation would not affect the authority of any other Federal agency which has jurisdiction over certain activities which are in some way relevant to recombinant DNA. Specifically, no portion of the Occupational Safety and Health Act would be superceded by the Recombinant DNA Act. Where appropriate, other Federal agencies would be expected to cooperate with DHEW in carrying out is responsibilities under this Act.

Extension of the Safety Requirements of the NIH Guidelines to All Public and Private Entities

The standards described in section II (Containment) and section III (experimental guidelines) of the current NIH Guidelines would apply to all public and private recombinant DNA activities. As section IV (roles and responsibilities) is intimately tied to the NIH granting process, it is inappropriate as a general provision. Thus, under the proposed legislation the Secretary of Health, Education and Welfare is to promulgate administrative regulations within 90 days of enactment, without regard to the provisions of the Administrative Procedures Act.

Registration of activities

The proposed legislation would require each individual or entity engaged in a recombinant DNA activity to report in writing to the

Secretary of DHEW a description of such activity and assurances that he will comply with the requirements under the legislation in carrying out such activity.

Revisions and exemptions

Revisions in the requirements are to be accomplished by regulation, with a public comment period.

Exemptions may be granted by order of the Secretary, subject to any conditions he may prescribe, for activities determined to pose no significant risk to health or the environment, or for specific risk assessment studies supported by the Secretary.

Inspection and enforcement

The Secretary of HEW is given broad inspection authority to ensure that all recombinant DNA activities are conducted according to the NIH standards. He may delegate much of this responsibility to local (biohazard or biosafety) committees at his discretion.

The proposed legislation spells out what constitutes a "prohibited act" and allows the Secretary to suspend HEW grant funds for violations, to impose a civil fine of $5,000, or to seek an injunction in the courts to restrain or enjoin activities done in violation of the requirements. U.S. district courts shall have jurisdiction over civil actions, including those brought for the seizure or destruction of material involved in a violation of the law.

Effect on State and local requirements

Under the proposed legislation, a State or local government could enact stricter laws which would supersede the requirements of this Act if it can be shown that such action is necessary to protect health or the environment, taking into account local conditions. That is, a State or local government would have to demonstrate that the requirement under the proposed legislation provide inadequate protection of health or the environment in the context of a particular local situation.

Training and studies

The Secretary would be authorized to conduct and support training programs in safety techniques for persons engaged in recombinant DNA activities and required to conduct and support risk assessment studies.

Study Commission

A 13-member study commission would be established to evaluate Federal policy on Recombinant DNA activities and to investigate the long term applications of gene-splicing technology. The commission could consider all aspects of genetic manipulation rather than being limited to the narrow scope of recombinant DNA activities. The commission is to complete its studies in thirty months and recommend appropriate Federal action.

BACKGROUND

On January 19, 1977, Representative Ottinger submitted House Resolution 131 calling for the promulgation of regulations governing all recombinant DNA research by the Secretary of Health, Education and Welfare, under section 361 of the Public Health Service Act. On February 7, 1977, Representative Ottinger introduced H.R. 3191,

the "DNA Research Act of 1977" and on February 16, 1977, Representatives Ottinger, Badillo, Bedell, Corrada, Dellums, Duncan, Edwards, Gilman, Howard, Hughes, Jeffords, Kostmayer, Leach, Lehman, Mikva, Moakley, Neal, Richmond, Roybal, Scheuer, Simon, Steers, Walgren, Waxman, and Burke introduced H.R. 3591 and H.R. 3592, both identical to H.R. 3191.

Representative Solarz introduced H.R. 4322, the "Commission on Genetic Research and Engineering Act of 1977", on March 1, 1977. Representatives Rogers, Maguire, Preyer, Scheuer, Waxman, Florio, Markey, Walgren, Carter and Madigan introduced H.R. 4759, the "Recombinant DNA Research Act of 1977", on March 9, 1977.

Hearings on these bills were held by the Subcommittee on Health and the Environment on March 15, 16 and 17, 1977. On April 6, 1977, the administration's proposal, the "Recombinant DNA Regulation Act", was introduced as H.R. 6158 by Representative Rogers by request. Subsequently, a Subcommittee Discussion Draft was prepared on the basis of a subcommittee markup session on May 2, 1977, introduced by Representative Rogers on May 24, 1977, as H.R. 7418, the "Recombinant DNA Act". As a result of markup sessions in June, 1977, the subcommittee ordered reported a clean bill, H.R. 7897, introduced on June 20 by Representatives Rogers, Preyer, Scheuer, Waxman, Florio, Maguire, Markey, Ottinger, Walgren, Carter, Madigan, and Skubitz.

The Committee on Interstate and Foreign Commerce considered H.R. 7897 in markup sessions in September and October, 1977, agreeing to several amendments. However, the markup of H.R. 7897 was never completed and the bill was not reported by the Committee.

Representative Staggers introduced H.R. 10453 on January 19, 1978. This bill was not considered further. On February 28, Representatives Staggers and Rogers introduced H.R. 11192, which was subsequently considered by the Committee on Interstate and Foreign Commerce. On March 15, 1978, H.R. 11192 was considered, amended and ordered reported by the Committee by a vote of 17 for and 6 against.

NEED FOR THE LEGISLATION

Nearly 5 years ago, at the Gordon Conference on Nucleic Acids, scientists reported the first results of a revolutionary technique in genetics and molecular biology, allowing the transplantation of genes from one organism into living cells from a completely unrelated species. By this method, DNA (deoxyribo-nucleic acid), the carrier of genetic information in all living cells and many viruses, is isolated from two or more sources, broken and recombined in the laboratory. This recombinant DNA is then inserted into a living host cell, in which perhaps all of the genes contained within the recombinant DNA molecule may be expressed. In this way, frog genes, insect genes, and animal genes including the gene coding for insulin have been introduced into bacteria. By combining the DNA of certain animal viruses with "foreign" DNA, novel genes may also be introduced into cultered mammalian cells. Similar methods allow the transplantation of genes into plant cells.

The scientists at the 1973 Gordon Conference, while recognizing the exceptional value of this technique as a research tool in the study of genetic mechanisms as well as a means to manufacture by a simple

and inexpensive method complex biologicals needed in medicine, also expressed concern that there may be hazards associated with altering the genetic make-up of cells, particularly microorganisms which might be infectious. Because such modified organisms would never have existed in nature, and, therefore, might have unpredictable properties, perhaps even posing a serious threat to human health or the environment, these scientists called for the formation of a study committee to recommend specific actions and develop research guidelines.

As an eventual result of this initiative, the National Institutes of Health (NIH) released, on June 23, 1976, Guidelines for Research Involving Recombinant DNA Molecules. These guidelines prescribe safety techniques to be followed and define different levels of physical and biological containment which would be imposed on each experiment, according to the degree of potential hazard presumed to be associated with each such recombinant DNA activity. The guidelines also specify that approval of each project on safety grounds and of the containment facilities available must be given by a local biohazards committee before a research grant to carry out such a project would be awarded by NIH.

The NIH Guidelines, however, are not regulations. They can only be imposed as binding upon NIH employees, or those receiving grant or contract funds from NIH. Thus, while the NIH Guidelines may serve as a model for the safe conduct of recombinant DNA research generally, they have no official standing in the other Government agencies supporting or engaged in recombinant DNA research, in state or privately supported research, or in private industry. Some Federal agencies (NSF, ERDA) have adopted the guidelines for their own grantees while others (USDA) support them only in spirit.

It is generally agreed that if recombinant DNA research and technology do indeed pose potential hazards to health or the environment, then safety requirements imposed upon such activities should not depend on whether or not NIH, or the Federal Government, is directly involved. Thus, a number of State and local governments beginning with Cambridge, Mass., in 1976, have considered imposing comprehensive recombinant DNA regulations of their own. However, such local actions present the possibility of safety regulations which could differ considerably from State to State, or city to city.

Recognizing the need for uniform and comprehensive safety regulations for recombinant DNA research and technology, an interagency committee chaired by Dr. Donald Fredrickson, Director of the National Institutes of Health, deliberated for several months as to whether or not any Federal agency had the statutory authority to promulgate comprehensive regulations for recombinant DNA activities. In March 1977, just prior to the recombinant DNA hearings held by the Subcommittee on Health and the Environment, the interagency committee announced its conclusion that while some existing laws, such as the Public Health Service Act and the Toxic Substances Control Act, allowed limited regulatory authority to promulgate safety regulations for recombinant DNA activities, none was sufficiently comprehensive. This committee proposed to Congress that legislation be enacted to regulate all recombinant DNA activities.

At the hearings held by the Subcommittee on Health and the Environment on March 15, 16 and 17, 1977, there was nearly unanimous agreement that comprehensive Federal legislation should be enacted,

although there was considerable disagreement as to the degree of possible or probable hazard posed by recombinant DNA activities, as well as just how restrictive the legislation should be. Most witnesses, however, believed that the safety standards set forth in the NIH Guidelines would, if properly enforced, provide adequate protection to public health and the environment.

During the spring and summer of 1977, there was growing opposition to legislation to regulate recombinant DNA activities among certain scientists. The basis for the opposition, was, in part, the publicizing of new data demonstrating that the possibility of rendering *E. coli* K–12 an epidemic pathogen by the insertion of recombinant DNA was virtually nonexistent. Furthermore, the recent development of plasmid vectors with very low transfer frequencies would make the inadvertent transfer of recombinant DNA to known pathogens very unlikely. These data were elucidated in a letter to Dr. Fredrickson from Dr. Roy Curtiss III, then a member of the NIH Recombinant DNA Molecule Program Advisory Committee, and discussed further at an NIH sponsored workshop on risk assessment held at Falmouth, Mass., on June 21–22, 1977.

Dr. Sherwood Gorbach, chairman of the Falmouth workshop, stated in a letter to Dr. Fredrickson summarizing the discussion, "The participants arrived at unanimous agreement that *E. coli* K–12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts." Since most, but by no means all, recombinant DNA activities use the *E. coli* K–12 host, some scientists drew the conclusion that not only was legislation to regulate recombinant DNA activities unnecessary, but that the NIH Guidelines themselves were largely superfluous. However, such a conclusion was not generally shared by the participants at Falmouth. Dr. Bruce Levin, a Falmouth participant wrote, also in a letter to Dr. Frederickson, ". . . this (consensus) is a very comforting conclusion, but it is only part of the story. There remains the possibility that recombinant DNA carried by the "safe" hosts could be transferred to more invasive strains of *E. coli*, other enteric bacterial species or even the somatic cells of their metazoan hosts." In fact, the Falmouth participants concluded that more feeding experiments were necessary to adequately assess the transfer of DNA plasmids from *E. coli* K–12 to other strains. There was little or no discussion of a number of other potential hazards of recombinant DNA manipulations, including animal virus-mammalian host cell combinations, or of plant host-vector combinations. Dr. Levin concludes his letter, "I don't believe that evidence available through existing efforts at risk assessment is sufficient to justify a relaxation of the current NIH Guidelines on recombinant DNA research or of the efforts to enforce them". There was general consensus at Falmouth on the continued need to observe the NIH Guidelines.

It is the view of the committee that as long as there remain areas of recombinant DNA research where potential hazards are recognized to the degree that the best informed scientists agree that safety guidelines should be observed, legislation is necessary to extend such safety standards to all public and private parties, and to provide a means to enforce them. However, the committee recognizes that as data on the relative safety of recombinant DNA activities accumulate, the stringency of particular standards should be changed to reflect the best

currently available evaluation of the degree of risk associated with each particular type of manipulation or host-vector combination. In fact, the NIH Recombinant DNA Molecule Program Advisory Committee has proposed changes in the Guidelines based, in part, upon the conclusions of the Falmouth workshop. The revised guidelines are expected to officially replace the 1976 guidelines by June 1978.

The committee considers it important to make the distinction between the nature of the safety standards, and whether or not there exists a need to impose the safety standards by legislation. In the committee's view, a need now exists to establish by law a regulatory authority which will permit the imposition of the NIH containment standards and experimental guidelines on all recombinant DNA activities which may pose a risk to health or the environment.

Because of the possibility of rapid advancement in our understanding of the potential hazards presented by genetically modified organisms, a two-year interim control bill is proposed. It is understood that Congress will re-evaluate the need for safety guidelines and the need to require them by law in approximately one and a half years after enactment, basing its actions on the recommendations of the study commission and the performance of the Department of Health, Education, and Welfare in implementing this act. It is to be borne in mind, however, that legislation is not a direct response to perceived possible hazards but to the fact that the NIH Guidelines only apply to a fraction of the recombinant DNA activities being conducted. The NIH Guidelines are the primary response to potential hazards and, therefore, legislation is justified only to the extent that safety guidelines are necessary.

The need for legislation has been endorsed by the Inter-Society Council for Biology and Medicine, which includes a large number of biological and medical professional societies, the American Association of Universities, and the Director of the National Institute of Health. They generally support the provisions of H.R. 11192.

The following is a summary of the arguments for the need for Federal legislation to regulate recombinant DNA activities:

(1) Safety standards for the protection of health or the environment from the hazards of recombinant DNA research and technology should extend to all parties engaged in such activities.

(2) Uniform Federal regulations are needed to prevent widely varying state and local regulations.

(3) Safety standards for large-scale and manufacturing processes involving recombinant DNA are not now covered in the NIH Guidelines, and should, therefore, by provided by law.

(4) The health and safety of personnel working with recombinant DNA must be protected by law.

(5) Uniform Federal regulations will facilitate the United States' role in the development of international safety standards for recombinant DNA research and technology.

COST OF LEGISLATION

Although the proposed legislation contains no line-item authorization of appropriations, the Department of Health, Education, and Welfare estimates that the following costs will be incurred by the Department in carrying out the functions assigned to it by H.R. 11192.

2-Year cost projections—H.R. 11192 Recombinant DNA Act

[Dollars in millions]

	1979	1980
Number of positions in HEW	50	75
Projected cost, Title I	$3.0	$4.5
Projected cost, Title II	.5	.5

These projections are based upon the current 200 laboratories now using recombinant DNA techniques, and the 300 projected by the end of fiscal year 1978. This number is expected to grow significantly in the near future.

The required staff positions include those involved in developing and conducting training programs for the approximately 1,500 scientists and technicians soon to be involved in recombinant DNA research, to handle paperwork involved with the registration of activities, and to assist the Secretary and the NIH Recombinant Advisory Committee in carrying out its duties to develop and review safety standards and then respond to inquiries from the scientific community regarding interpretation of the regulations and from the public regarding the safety and usefulness of recombinant DNA activities, and for inspectors and other general support staff.

The estimated cost of the study commission is listed separately.

SECTION-BY-SECTION SUMMARY OF H.R. 11192

Title I—Interim Regulation of Recombinant DNA Activities

Definitions (section 101)

Section 101 of the bill defines the term "recombinant DNA" explicitly and operationally as it is done in current NIH Guidelines. "Recombinant DNA activity" is defined as the possession in a State of recombinant DNA and any activity (including research and transportation) undertaken for the production of recombinant DNA.

Extension of the recombinant DNA guidelines (section 102)

Section 102(a) of the bill provides for the extension of the requirements of sections II (Containment) and III (Experimental Guidelines) of the NIH Guidelines to all recombinant DNA activities beginning on the tenth day after the date of enactment and ending twenty four months after such day. Before the expiration of the ten-day period the Secretary of HEW is required to publicize and make available the requirements of sections II and III of the Guidelines. The Secretary is authorized to amend the requirements, in accordance with the Administrative Procedure Act, if he determines that such an amended requirement would be sufficient for the protection of health and the environment.

Section 102(b) authorizes the Secretary to exempt from the requirements any recombinant DNA activity which he finds does not present a significant risk to health or the environment.

Section 102(c) requires each individual or entity which is responsible for the conduct of any recombinant DNA activity or which will be responsible for such an activity to be commenced during the period the guidelines are in effect to report to the Secretary such individual's or entity's name, a description of such activity, an identification of the place or places in which such activity is or will be conducted, and

assurances satisfactory to the Secretary that such activity will be carried out in accordance with the requirements of the guidelines.

Section 102(d) requires the Secretary within 90 days of the date of enactment to issue regulations for the administration of the requirements of the proposed legislation.

Prohibited acts and penalties (section 103)

Section 103(a) prohibits any person from conducting any recombinant DNA activity in violation of any requirement of section 102 of the bill; moving recombinant DNA in violation of an order issued under section 105(c) (administrative detention); or failing or refusing to establish or maintain records, make reports or provide information, or permit entry to instruction as required by the proposed legislation.

Section 103(b) provides that any person who violates section 103(a) would be liable for a civil penalty of up to $5000 for each violation. Each day such a violation continues would constitute a separate violation.

Section 103(c) authorizes the Secretary, in instances in which a person has violated section 103(a) in carrying out a project funded by a grant from HEW, to cancel such grant or withhold payments under such grant until he determines such person will carry out such project in accordance with the requirements of the guidelines.

Injunction authority—emergency procedure (section 104)

Section 104(a) confers upon U.S. district courts the jurisdiction over civil actions to restrain violations of section 103(a). Such actions are to be brought in the judicial district where the violation occurred or where the defendant transacts business. In such actions, process may be served on defendants and subpoenas served in any judicial district.

Section 104(b) confers upon U.S. district courts jurisdiction over civil actions for (1) the seizure or destruction of recombinant DNA, or material used in a recombinant DNA activity, which was involved in a violation of section 103(a) or which presents or may present a significant risk to health or the environment or (2) any other appropriate relief to prevent the production or movement of such recombinant DNA or material. Such actions are to be brought in the judicial district in which the recombinant DNA or material is found.

Inspections (section 105)

Section 105(a) authorizes individuals designated as inspectors by the Secretary for purposes of enforcement of the requirements of section 102 to enter and inspect any place in which a recombinant DNA activity is being conducted or in which the inspector has reasonable grounds to believe such an activity is being conducted. Such an inspection is to be conducted during normal business hours (if any) of the place, and may extend to all things in the place bearing on whether the activity is being conducted in accordance with the applicable requirements. Before entering a place, an inspector is to present appropriate credentials and a written notice to the person in charge and clearly inform such person of his authority. Upon completion of any inspection, the inspector is to provide the person in charge with a preliminary report summarizing any condition or

practice which indicates a violation of the applicable requirements. Within 30 days the inspector is to prepare a final written report.

Section 105(b) requires a person in charge of a place inspected, upon request of the inspector, to provide samples of recombinant DNA or materials used in or produced by any recombinant DNA activity conducted in such place to enable the inspector to determine if the applicable requirements are being met.

Section 105(c) authorizes an inspector to order recombinant DNA or materials used in or produced by any recombinant DNA activity detained for a period not to exceed 20 days if he has reason to believe it is involved in a prohibited act under section 103(a) or presents a significant risk to health or the environment. If the Secretary determines a longer period is necessary in order to institute a civil action under section 104(b), he may authorize a detention period of up to 30 days.

Section 105(d) provides that no inspector shall be required to obtain a search or inspection warrant before inspecting a place.

Section 105(e) provides that an individual who is engaged in or has a direct financial interest in a project involving a recombinant DNA activity cannot be designated as an inspector of such project.

Effect on State or local requirements (section 106)

Section 106(a) provides that (except as authorized under section 106(b)) no State or political subdivision thereof may establish or continue in effect any requirement for the regulation of recombinant DNA activities.

Section 106(b) establishes conditions and procedures under which States and political subdivisions thereof may prescribe requirements with respect to recombinant DNA activities. It requires the Secretary, upon application, after notice and opportunity for an oral hearing, and after considering local conditions, to issue an order exempting a State or local requirement from subsection (a) if (1) the requirement is the same as, or more stringent than, a requirement under section 102(a) and (2) the requirement is necessary to protect health or the environment. The oral hearing is to be commenced not later than 60 days from the date the application is submitted. The presiding officer at the hearing is to make a written recommendation to the Secretary respecting approval of the application. Within 60 days of the conclusion of the hearings or 120 days after submission of the application, whichever occurs first, the Secretary must approve or deny the application. The Secretary's decision must be in writing and, if a hearing was conducted, the decision must contain the recommendation made by the presiding officer, and must include a complete statement of the reasons for the Secretary's decision.

Training and studies (section 107)

Section 107(a) authorizes the Secretary to conduct and support training in the safe handling of recombinant DNA.

Section 107(b) requires the Secretary to conduct or support on a continuing basis studies assessing the risks to health and the environment of recombinant DNA activities. In addition, it authorizes the Secretary, by order, to make the requirements of section 102 inapplicable to such risk assessment studies. Such orders are to be published

in the Federal Register together with a statement of the basis for the order.

Relationship to other Federal laws (section 108)

Section 108(a) specifies that title I shall not affect the authority of any Executive Agency to regulate recombinant DNA activities under any other Act.

Section 108(b) establishes that the Secretary shall not be deemed to be exercising statutory authority under section 4(b)(1) of the Occupational Safety and Health Act of 1970, in exercising any authority under title I of this act.

Title II—Commission for the Study of Research and Technology Involving Genetic Manipulation

Section 201 provides for the establishment of a thirteen member Commission for the Study of Research and Technology Involving Genetic Manipulation. The members of the Commission are to be appointed by the Secretary of HEW from individuals distinguished in the fields of medicine, law, ethics, the biological, physical, and environmental sciences, philosophy, humanities, health administration, government and public affairs.

Section 202 sets forth the duties of the Commission which include (1) the conduct of a study of Federal policy regarding activities involving the genetic modifications of organisms and viruses, and (2) a study of the long-term consequences of the development of a technology capable of accomplishing the genetic modification of organisms and viruses.

Section 203 requires the Commission, in carrying out its duties, to hold public hearings as appropriate, and requires the head of any U.S. department or agency to furnish to the Commission, upon its request, information necessary to enable the Commission to carry out its duties.

Section 204 requires the Secretary, within 18 months after the date of enactment, to report to the Congress the preliminary results of he Commission's study with respect to Federal policy regarding activities involving the genetic modification of organisms and viruses. It further provides that the Commission, within 30 months after the date of enactment, is to complete its studies and make recommendations to the Congress, the President, and appropriate Federal agencies regarding action the Commission determines should be taken to promote, regulate, or review activities involving the genetic modification of organisms and viruses. Finally, it provides that the Commission shall terminate within 60 days of the date upon which is completed its studies and made its recommendations.

ANALYSIS OF SECTIONS AND COMMITTEE VIEWS

Section 1. Short title

The first section of H.R. 11192 as reported by the Committee, provides that this legislation may be cited as the "Recombinant DNA Act".

Section 2. Findings

The purpose of these findings is not only to formally recognize that recombinant DNA techniques may provide an extremely important

research tool and may ultimately lead to many practical benefits to mankind, and are accompanied by uncertainties regarding the risks posed to health and the environment by altering the genetic make-up of an organism. The findings also establish the constitutional grounds to regulate recombinant DNA activities under the commerce clause of the constitution, which permits the Federal Government to regulate any activity affecting interstate commerce.

Therefore, paragraph (1) acknowledges that research and other activities involving recombinant DNA will improve the understanding of fundamental biological processes, and paragraph (2) cites the potential benefits to society which may accrue from the pursuit of recombinant DNA activities.

Paragraph (3) recognizes that while actual hazards have not been demonstrated, uncertainties exist regarding the extent to which recombinant DNA, or organisms or viruses modified by recombinant DNA may present a risk of injury to health or the environment. The argument is then made that if such a risk exists (without saying what the magnitude of the risk may be), then the organisms or viruses which pose such a risk may spread quickly and without warning to persons, agricultural plants and products, and other items in or affecting commerce. It is this latter statement which argues that if such a risk exists, however small, then interstate commerce will be affected.

Paragrph (4) further argues that until the uncertainties regarding the potential hazards of genetically modified organisms are resolved, the public interest requires that the health and welfare of the population of the United States be protected from such hazards, and that commerce is dependent upon such protection being provided. Thus, it follows from the above that the integrity of interstate commerce requires the protection of public health against any risk posed by recombinant DNA activities.

The final paragrph of the findings (5) then states that in order to provide the protection of health required to keep interstate commerce from being adversely affected, any activity involving organisms or viruses containing recombinant DNA must be subject to control. Thus the constitutional argument for regulation of recombinant DNA activities is completed.

It should be emphasized that the findings do not represent the collective editorial position of the Committee with respect to the relative importance of risks and benefits. Paragraph (3) is a conditional statement recognizing that the risks posed, by at least some recombinant DNA activities are uncertain, and that if indeed the possibility exists that dangerous organisms could be created by recombinant DNA techniques, then it is incumbent upon Congress to regulate such activities, since the health of the population and, therefore, interstate commerce, will be adversely affected. Since most experts agree that it is very likely possible to create a hazardous organism or virus by recombinant DNA methods, even though it may be highly improbable, the argument of paragraph (3) must be considered sound. Only if and when it can be demonstrated that recombinant DNA—containing organisms could not possibly pose a health or ecological hazard would the argument that to regulate such activities is constitutional be considered invalid.

TITLE I—INTERIM REGULATION OF RECOMBINANT DNA ACTIVITIES

Section 101. Definitions

(1) DNA

DNA is used throughout the proposed legislation as the abbreviation for deoxyribonucleic acid, the molecular entity which is the primary site of genetic information for all living organisms and a large fraction of viruses.

(2) Recombinant DNA

Subparagraph (A) contains an operational definition of recombinant DNA, designed to be consistent with that in the proposed revisions to the NIH Guidelines. In order to be considered recombinant DNA, a DNA molecule must consist of two or more DNA segments which are joined together outside of living cells and must have the capacity to enter and propagate within a living cell, either autonomously or after integration with the cell's genome. This definition is intended primarily to cover those molecules formed by the site specific recombination of double stranded DNA segments obtained as products of restriction endonuclease digestion of larger DNA molecules. However, this definition also includes recombinant DNA molecules which contain chemically synthesized segments or which are formed using enzymes other than restriction endonucleases and DNA ligase.

Because replication products of recombinant DNA molecules are presumably identical to the parent molecules, but formed *inside* living cells, they are also to be considered recombinant DNA for the purposes of legislation, as specified in subparagraph (B). That is, all of the cells in a bacterial clone resulting from a single cell containing recombinant plasmid DNA, are considered to be cells containing recombinant DNA.

It is recognized that some recombinant DNA molecules may not represent a unique or unusual set of genes to be propagated in a particular host cell, and thus not create a potentially hazardous organism. However, it is the Committee's intent that any exclusions for obviously safe host-vector combinations be included under section III of the NIH Guidelines, or by exemptions from the requirements of this title granted under section 102(b).

(3) Recombinant DNA activity

The phrase "recombinant DNA activity" is used throughout the recombinant DNA Act to denote all uses of recombinant DNA, including research, transportation, possession or production.

(4) Public entity

An important clause in definition (3), "recombinant DNA activity", defines as included in this Act any activity "undertaken in a state by any individual or public or private entity". The term "public entity" is defined here as any Federal, state or local government entity. This

provision legally establishes inclusion of all private and governmental recombinant DNA activities within the legal jurisdiction of the United States under the Recombinant DNA Act.

(5) Secretary

The term "Secretary" means the Secretary of Health, Education, and Welfare.

SECTION 102. EXTENSION OF THE RECOMBINANT DNA GUIDELINES

102(a). Safety requirements

The committee recognizes the difficult and time-consuming task undertaken by the National Institutes of Health in carefully considering the technical details of all anticipated recombinant DNA activities, reviewing all available data in order to assess the possible risk posed by each particular activity, and in developing explicit physical and biological containment requirements and experimental guidelines for the conduct of research and other activities involving recombinant DNA molecules. It is the consensus of the scientific community that these safety guidelines represent an appropriate response to the uncertainties presented by genetically modified organisms, and that they provide a substantial margin of safety to both workers and the public.

Therefore, paragraph (1) specifies that beginning on the tenth day after enactment, all recombinant DNA activities must be carried out in accordance with the safety requirements described in section II ("Containment") and section III ("Experimental Guidelines") of the NIH Guidelines, unless exempted from these requirements by the Secretary as specified elsewhere in this act (section 102(b) or section 107(a)(2)). The 10-day period after the day of enactment is included to allow time to provide notice to the public that such requirements will be in effect, as required by paragraph (3). The Secretary must publish the requirements in the Federal Register before the expiration of the 10-day period. These provisions are to remain in effect for a 2-year period; Congressional action would be required to extend them beyond the 2-year period.

Under the proposed legislation, sections II and III of the NIH Guidelines in effect at the date of enactment would become the safety standards for the conduct of any recombinant DNA activity. That is, if the expected revisions in the guidelines are put into effect before the legislation is signed into law, then it is sections II and III of the revised NIH Guidelines which apply.

Paragraph (2) specifies that after the date of enactment, the Secretary may revise the above requirements by regulation. Such regulations must be promulgated in accordance with the Administrative Procedure Act (section 553 of title 5, United States Code), requiring the publication of proposed changes and a public comment period. It is recognized by the committee that, while not required by law to do so, NIH has published all proposed revisions of the guidelines in the Federal Register, and has, in addition to a public comment period, held public hearings on the proposed revisions. The committee commends the efforts of NIH to inform the public of its actions regarding recombinant DNA policy and to enable the public to participate in

the decisionmaking processes by which the revisions are made. It is expected that this spirit of public involvement will be continued by the Secretary following passage of the Recombinant DNA Act.

Revisions in the safety standards are to be made according to the legislative standard that the safety requirements in effect after amendment will be sufficient to protect health or the environment. This standard, then, must always be considered by the Secretary in any revisions to be promulgated under this section.

102(b) Exemptions

If a particular recombinant DNA activity or class of such activities is found by the Secretary to present no significant risk to health or the environment, he may exempt it from the requirements of this section. An order of the Secretary is not required by the Administrative Procedure Act to be published in the Federal Register as a proposed rule, and, unlike regulations, may be put into effect in a relatively short time. Such an order is, however, subject to appeal on the grounds that the statutory standard upon which the order was based was not met or was incorrectly applied.

The power to exempt activities would also be considered implicit in section 102(a)(2) allowing the Secretary to revise the requirements by regulation. That is, if an activity is considered to pose no significant risk to health or the environment, then the requirements in effect after exempting such an activity should still be sufficient to protect health or the environment.

It is the intent of Congress that section 102(b) be used to exempt activities only in cases where there is a clear consensus that a particular recombinant DNA activity does indeed present no significant risk to health or the environment. The term "significant risk" should be interpreted conservatively in view of what is considered to be an acceptable or significant risk in other regulations and safety standards authorized under other statutes designed to protect public health or the environment.

If the assessment of potential hazards presented by an activity remains unresolved, or controversial, even if it appears to be somewhat less hazardous than previously believed, then subsection 102(a)(2) should be used for the purpose of revision rather than subsection 102(b). The Secretary may, however, include whatever terms or conditions he considers appropriate with his order of exemption. Therefore, in instances where the safety of an activity appears to be well established, but where minor uncertainties remain, the Secretary could deal with such activities with a qualified order in which the remaining uncertainties were addressed.

While it is recognized that it is often important for the Secretary to act quickly and be responsive to new data in a rapidly changing field, it is the committee's intent that the public be informed of all intended action and allowed to express its views, to an extent feasible which would not delay needed changes in the safety standards. It is also the committee's desire that while the regulations and safety standards in effect under this act be sufficient to protect health or the environment, any superfluous requirements should be removed as soon as possible after it becomes apparent that they are no longer necessary. Thus, the Secretary should use considerable care and discretion in determining which activities would be proper candidates for the easing of the

stringency of the safety requirements by revision under subsection 102(a)(2) and which should properly be exempted under subsection 102(b).

102(c). Registration

All recombinant DNA activities in progress on the tenth day after the date of enactment must be registered with the Secretary within ten days from the date the administrative regulations promulgated under subsection 102(d) go into effect. Any activity which is undertaken subsequent to the date of enactment must be registered at the time it is commenced. Such registration is to be carried out in accordance with the administrative regulations promulgated by the Secretary under subsection 102(d).

Such registration requires that the name of the individual or entity responsible for the conduct of a recombinant DNA activity, identification of the place or places where such activity is to be conducted, a description of the activity and assurances to the Secretary that the safety requirements in effect under this act will be observed, be reported to the Secretary.

The degree of detail required for the description of each recombinant DNA activity is left to the discretion of the Secretary. However, it is the committee's intent that such description include sufficient technical information to enable an independent reviewer to determine which provisions of sections II and III of the NIH Guidelines would apply to that particular activity. It must also enable a technically competent reviewer to estimate the potential hazard to the health of both workers and the general public and the risk to the environment, to the extent that current knowledge of potential hazards would permit such a judgment. While the overall design of the activity should be included, it is not the intent of the Committee that details of research designs and protocols not relevant to safety consideration be required to be submitted.

It is recognized that, in some instances, information relevant to risk and safety may be proprietary or a registrant may wish such information to be held in confidence. Therefore the administrative regulations promulgated under subsection 102(d) should include such provisions as necessary to protect the disclosure of proprietary data. Any lists of registered recombinant DNA activities made available to the public or published by the Secretary need not include confidential or proprietary information.

102(d). Administrative regulations

The Secretary must, within 90 days after enactment, issue proposed regulations for the administration of the requirements of section 102 and section 105 (Inspections). At present, section IV of the NIH Guidelines (Roles and Responsibilities) specifies how sections III and IV will be administered to NIH grantees. While the regulations to be promulgated under this section may supersede section IV, it is intended that this section continue to govern the administration of the NIH safety standards for those activities which are currently under the NIH Guidelines, at least until such time that the regulations promulgated by the Secretary under section 102(d) become final.

It is the view of the committee that the appropriate portions of the administrative requirements of section IV of the NIH Guide-

lines are a reasonable model upon which the Secretary could base administrative regulations. In particular, the current practice in the NIH Guidelines of delegating to local biohazards committees most of the responsibility for the inspection of facilities and the approval of the specific safety requirements appropriate to each project or activity is an effective and relatively inexpensive administrative mechanism. Furthermore, most institutions where recombinant DNA activities are or will be conducted already have a biohazards committee in place.

The regulations under this section should, therefore, include guidelines respecting the membership of biohazards committees including the number of committee members, the method by which members are selected and the inclusion of public members. These guidelines should also address potential problems of conflict of interest between biohazards committee members and activities in which they have a direct or financial interest.

The committee expects that the NIH Recombinant DNA Molecules Program Advisory Committee will continue its current function of continually examining and updating the content of sections II and III of the guidelines, of approving new safe hosts and vectors and generally providing technical advice on policy matters. The regulations under this section should, however, include provisions respecting the diversity of the membership of this committee in order to guarantee representation on the committee of the full range of technical expertise needed to properly evaluate potential hazards posed by recombinant DNA activities and to design appropriate safety standards. Since the perspective of non-scientists has been found to be of value on the current Recombinant Advisory Committee, such regulations should also require that some members be appointed from non-scientific disciplines.

Since the individuals working directly on recombinant DNA activities would generally be at the greatest risk, should any hazards be presented by the conduct of such activities, the committee expects the Secretary to include in the regulations promulgated under this subsection provisions to reduce the risk of injury to such individuals as much as possible. Such requirements might include laboratory safety training courses or examinations, information to be given to workers concerning the nature of the risks presented, monitoring for indicators of possible infection, where appropriate, and guidelines concerning the type and frequency of medical examinations. Such personnel safety provisions would be particularly important in the case of workers involved in manufacturing or mass production procedures who may not be trained scientists or research technicians.

It is the committee's intent that the administrative regulations address the problem of the protection of confidentiality of propriety or other data where appropriate. In order to make determinations as to the proper safeguards appropriate to each recombinant DNA activity in its jurisdiction, local biohazards committees may at times have access to information in this category. Members of local committees who are carrying out administrative duties under this act, would be doing so as agents of the Secretary and thus subject to section 1905, title 18, United States Code, making it a criminal offense for Federal employees to disclose trade secrets.

The administrative regulations to be promulgated under this subsection are exempted from the provisions of section 553 of title 5, United States Code, the Administrative Procedure Act. They are to take effect upon their publication in the Federal Register.

This method of rulemaking was chosen so as to establish administrative regulations as soon as possible after enactment, without the lengthy procedures involved in the promulgation of regulations according to the provisions of the Administrative Procedure Act. It is generally considered that since the administrative regulations per se do not deal with a potential hazard to health or the environment, there would be no perversion of the intent of the law to waive the Administrative Procedure Act. However, since the committee recognizes that there could well be public concern over even administrative regulations, the Secretary shall provide interested persons with an opportunity to present written comments, and may also provide an opportunity for the oral presentation of views and arguments. After consideration of the comments so received, the Secretary may by order make appropriate revisions in the regulations.

APPLICABILITY OF THE NATIONAL ENVIRONMENTAL POLICY ACT OF 1969

During its consideration of H.R. 11192, the committee deleted subsection 102(e) which provided that the National Environmental Policy Act of 1969 (NEPA) shall not apply to any action under title I of the bill. The committee believes such a statutory exemption from NEPA is both unnecessary and an unwise precedent. The elimination of subsection (e), furthermore, will not adversely affect the basic thrust of the proposed legislation—prompt application of the present NIH guidelines to non-NIH grantees.

Subsections 102(a)(1) (A) and (B) of the bill will make the sections II and III of the Guidelines initially applicable to all persons by operation of law, not through a rulemaking process by an administrative agency. NEPA's requirements, however, are applicable only to actions of Federal administrative agencies, and not to the Congress. Hence, NEPA would be inapplicable to the requirements of these subsections, i.e. the application of the guidelines either as they were published on July 7, 1976, or any revision thereof made prior to the 10th day after the date of enactment of this bill.

Moreover, under the Supreme Court's ruling in *Flint Ridge Development Co.* v. *Scenic Rivers Association of Oklahoma*, 426 U.S. 776 (1976), the requirements of NEPA could not serve to delay the issuance, under section 102(d) of the bill, of the regulations for the administration of the requirements made by section 102. In its *Flint Ridge* decision, the Supreme Court ruled that the mandatory limitation of 30 days imposed by the Interstate Land Sales Disclosure Act (ILSDA), was inconsistent with the NEPA's requirement of an environmental impact statement (EIS) because an EIS could not possibly be accomplished within 30 days, and hence made NEPA's EIS requirement inapplicable to the actions prescribed by the ILSDA. Subsection 102(d) of the committee bill requires the Secretary to promulgate effective administrative regulations within the 90-day period beginning on the date of enactment of this bill. Under the *Flint Ridge* decision, these initial administrative regulations may not be delayed

by otherwise applicable NEPA requirements. The Secretary should, of course, promptly proceed to prepare an EIS with respect to these regulations and complete it as early as possible. However, if the EIS is not completed within that 90-day period, the regulations shall then be promulgated notwithstanding the absence of the EIS. It is the committee's understanding that the Secretary will complete and file an EIS on all the guidelines and administrative regulations, as expeditiously as practicable, even after promulgation of the administrative regulations, and that such EIS will be considered in determining whether (and if so, how) to revise the initial requirements and administrative regulations.

Furthermore, NEPA would apply to any revisions either of the initial requirements promulgated under section 102(a)(2), or of the administrative regulations under section 102(d) of the Committee bill.

SECTION 103. PROHIBITED ACTS AND PENALTIES

103(a). Prohibited acts

Paragraph (1) of subsection (a) sets forth, for the purposes of any enforcement action which may be required, the stipulation that it is illegal to violate the requirements of section 102. Paragraph (2) prohibits the movement of any recombinant DNA or other material in violation of a detention order issued under section 105 (Inspections). Paragraph (3) establishes the requirement that it is illegal under the legislation to fail or refuse to (A) establish or maintain records, (B) make reports or provide information, or (C) permit entry or inspection.

103(b). Civil penalties

Paragraph (1) authorizes a civil penalty of up to $5,000 for each violation of subsection (a), where each day a violation continues is considered a separate violation. While the word "person" may be interpreted with some latitude by the courts, it is intended that the entity legally responsible for the conduct of a particular recombinant DNA activity be legally responsible for any fines assessed for a violation under this act. For example, if an assembly line worker in a pharmaceutical company were to violate some provision of section 102, his or her employer could be held legally responsible. Whether or not the individual would also be held responsible would depend upon the specific circumstances of the violation. In some instances, where a willful and knowing violation was committed by an individual, in spite of efforts by his or her employer to inform that person of the applicable requirements, then that individual might be held solely liable. Of course, prosecutorial discretion ultimately would resolve the issue on a case by case basis.

103(b)(2) provides that the Secretary shall assess a civil penalty by an order made on the record after an opportunity for a hearing in accordance with section 554 of the Administrative Procedure Act (Adjudications). A person against whom a civil penalty is to be assessed has fifteen days from the date of receipt of a written notice from the Secretary stating his proposal to issue such an order, in which to request a hearing on the order.

103(b)(3). Judicial review

The rights of a person who requested a hearing in accordance with paragraph (2) and against whom a civil penalty is assessed, are set forth in this paragraph. Such a person may file a petition for judicial review of such an order with the United States Court of Appeals for the District of Columbia Circuit or any other circuit in which the person resides or transacts business. Such a petition must be filed within 30 days from the date the order of assessment of a penalty was issued.

If a person fails to pay an assessment of a civil penalty, the Attorney General may, under paragraph (4), bring action in the appropriate district court of the United States to recover the amount assessed plus interest at prevailing rates.

103(c). Suspension or cancellation of grant payments

If anyone violates the provisions of subsection 103(a) in carrying out a project funded by a program administered by the Secretary, the grant may be cancelled by the Secretary or payments suspended until he determines that the project will be conducted in accordance with the applicable requirements of the committee proposal. The intent of this section is to provide an effective means of enforcement of the NIH safety standards for those research projects supported by NIH research grants, now comprising a substantial portion of all recombinant DNA activities. The sanction of withdrawing research support is, for the university-based research scientist, very severe and should provide a more appropriate deterrent to violations of the law for such individuals than the threat of a civil penalty. The Secretary must provide a reasonable opportunity for an oral hearing before taking action under this subsection.

This section does not permit the Secretary to take any action which would affect the payment of research grants made under any Federal program outside of the Department of Health, Education, and Welfare, or from any private source. However, it is the desire of the committee that other entities providing support for the conduct of recombinant DNA activities cooperate fully with the Secretary, should he request that action be taken against those whom he determines are in violation of subsection 103(a). If such cooperation were not forthcoming, then the Secretary would have no alternative but to assess a civil penalty or seek an injunction under subsection 104(a) of this Act to restrain such violations.

The use of penalties and sanctions in practice

Rather broad powers of enforcement are authorized in the Recombinant DNA Act to insure that appropriate safety standards will always be observed in the conduct of recombinant DNA activities. These include the authority to revoke or suspend grants awarded under DHEW programs, the authority to assess civil penalties, and injunction authority. Such powers are necessary for any regulatory act to be enforceable.

However, it is the intent of the committee that penalties and sanctions be administered carefully and with fairness to all concerned. In most instances where minor violations come to the attention of inspectors, usually members of a biohazards committee, a simple request should be made that the deficiency be corrected before further work may proceed. Further action by the Secretary should generally not

be necessary, as the cooperation of those conducting recombinant DNA activities is anticipated. Only in the case of repeated or serious violations, where those responsible for the conduct of recombinant DNA activities are clearly not cooperating with the inspectors or the biohazards committee, would formal action by the Secretary be desirable. In these cases, if the project involved were supported by Federal funds, the first action would be expected to be suspension of a research grant or a formal request by the Secretary to the entity sponsoring support of the activity to withhold funds. Permanent revocation of grant support should be considered a rather drastic punitive measure and reserved for flagrant violations.

The maximum penalties, however, must be severe enough to discourage a company or institution from proceeding with experiments which the Guidelines require to be conducted under a high level physical or biological containment in willful disregard of the safety requirements. If the only sanction under the law were a small civil fine, then it might well turn out to be more economical to conduct an activity in an ordinary laboratory and pay the penalties, rather than to construct a P–3 or P–4 facility. If such cases should arise the Secretary is expected to seek injunctions to restrain the violations immediately.

The assessment of all penalties is, however, expected to be done fairly, with the magnitude of the penalty appropriate to the nature and severity of the violation. It is not intended that the fear of maximum penalties become an impediment to engaging in recombinant DNA activities. In practice, it is expected that, as long as entities comply with requests of the Secretary and his agents, there would be no need to assess any monetary penalties, withdraw grant funds or seek injunctions in court in order to restrain violations.

SECTION 104. INJUNCTION AUTHORITY; EMERGENCY PROCEDURE

104(a). Injunctions

Civil action may be brought in the U.S. district court to restrain any "act, omission, or transaction" constituting a violation of section 478 (a). An injunction or restraining order would provide an additional means of enforcement of the requirements and regulations of the Recombinant DNA Act. Such action could be used to stop any illegal action in addition to or in lieu of the civil action described in 103(b), or the suspension of grant funds described in section 103(c). The continuance of such illegal action would then constitute contempt of court and subject the violator to contempt penalties, in addition to the civil penalties authorized in section 103. Such action would normally be brought by the Attorney General or local U.S. Attorney, and would generally, but not necessarily, be taken at the request of the Secretary.

The committee views this provision as one which citizens can use to ensure enforcement of the guidelines. In order to gain access to the Federal district court, all that need be demonstrated is that the plaintiff has suffered "some threatened or actual injury resulting from the putatively illegal action . . ." *Linda R. S.* v. *Richard D.*, 410 U.S. 614, 617, (1973). Thus, the committee intends that an individual living within reasonable proximity to a research facility in which recombinant DNA activity is being conducted would have standing to seek to enjoin the facility's alleged violations of the proposed legislation. In such an instance, the plaintiff would have alleged a sufficient per-

sonal stake in the outcome of the controversy to warrant invocation of Federal court jurisdiction. See *Warth* v. *Seldin*, 422 U.S. 490, 498–99 (1975) and *Simon* v. *Eastern Kentucky Welfare Rights Organization*, 426 U.S. 26 (1976).

104(b). Emergency procedure.

Civil action must be brought in the appropriate district court of the United States in order to seize or destroy any recombinant DNA or related material involved in a violation of section 103(a), or which may present a significant risk to health or the environment, or in order to prevent the production or movement of such hazardous material. Thus, any material impounded by an inspector which he believes to be hazardous, or involved in a violation of the safety standards, may only be permanently seized or destroyed by such a court order. It is the committee's intent that in any such proceeding, the best scientific judgment be utilized as to whether or not such material is truly hazardous, and whether or not its seizure or destruction is justified. Every attempt should be made to store any labile biological or chemical material impounded by an inspector under conditions which would prevent its degradation or inactivation.

SECTION 105. INSPECTIONS

105(a). Inspection procedure

In order to enforce the requirements of section 102, broad inspection authority is given to the Secretary.

Inspectors designated by the Secretary, including employees and agents of local biohazards committees, may enter and inspect any place or conveyance where recombinant DNA activities are conducted upon presentation to the owner or authority in charge appropriate credentials and a written notice, and after clearly informing him of their authority. Separate notification is required for each inspection. Inspectons must be made during normal business hours and are expected to be carried out in a reasonable manner. This means that inspectors are expected to respect the problems caused by biological contamination, the fragility of such scientific equipment and importance of conducting experiments without disturbance. Therefore, in implementing the inspection provision, the Secretary is expected to respect the need for minimum disruption of experiments and other activities in progress.

Inspection may extend to relevant equipment materials, containers, records, files, papers, processes, controls, and facilities bearing on whether or not a recombinant DNA activity is being conducted in accordance with the requirements of section 102.

The committee intends that inspections be carried out in as informal and unobtrusive manner as possible. The Secretary is encouraged to place most of the authority for local administration of the Act in the local biohazards committees. Thus, it is anticipated that most inspections will be carried out by members or agents of local biohazards committees, with direct agents of the Secretary performing inspections only in rare or unusual circumstanes, such as reports of repeated violations, problems within a local biohazards committee or where P–4 facilities were involved.

Upon completion of any inspection, and prior to leaving the location or conveyance where the recombinant DNA activity is being conducted, the individual making the inspection must give to the owner, operator, or person in charge a preliminary report summarizing any condition or practice which indicates a violation of any regulation or license requirement. A final written report must be submitted to the appropriate individual within thirty days of completion of the inspection.

In general, since most inspections are intended to be carried out by biohazards committees, it is expected that both the responsible investigator and the appropriate representative of the institution conducting the recombinant DNA activity would be informed immediately of any situations not in conformance with the requirements of this act.

The biohazards committee may require that the deficiency be corrected before the activity may proceed further, and may be empowered to do so by the Secretary under his authority to promulgate administrative regulations under section 102(d). However, it is expected that most investigators and responsible institutions or companies would act immediately to cooperate with requests of a biohazards committee and that formal action by the Secretary to enforce compliance with the provisions of this act under sections 103 and 104 would, in general, be unnecessary. It is anticipated that most violations would be of a minor nature and be handled informally by the biohazards committee. It should be borne in mind that a biohazards committee serving a particular institution, may also have additional powers granted to it by the institution over and above the requirements of the Recombinant DNA Act, in order to enforce institutional safety requirements.

The committee has carefully crafted this provision to insure that it does not depart from Fourth Amendment protections against unreasonable searches. *Camara* v. *Municipal Court*, 387 U.S. 523 (1967) and *See* v. *City of Seattle*, 387 U.S. 541 (1967) and subsequent cases have provided clear instructions to the Congress as to how to design a Federal warrantless inspection statute that accomplishes its purposes as a crucial part of an effective regulatory mechanism without intruding on Fourth Amendment protections. See *Colonnade Corp.* v. *United States*, 397 U.S. 72 (1970), *United States* v. *Biswell*, 406 U.S. 311 (1972), and *Almeida-Sanchez* v. *U.S.*, 413 U.S. 266 (1973). From these cases can be culled four considerations utilized by the Supreme Court in determining whether an administrative inspection authorized by Federal statute is constitutional:

(1) was it preceded by adequate notice to the person in charge as to the identity of the persons conducting the inspection and the legal basis for the action?

(2) was the inspection carefully limited in time, place and scope?

(3) was the inspection of central importance to a valid Federal purpose?

(4) is there a long history of regulation of the inspected industry?

Clearly, the inspection authority meets three of the four tests of *Colonnade*, *Biswell*, and *Almeida-Sanchez*. First, inspectors are authorized to enter and inspect laboratories only after presenting appropriate credentials and a written notice to the person in charge of the laboratory and clearly informing such person of the authority to inspect. Second, inspections may only be made during normal business

hours of the laboratory and may extend only to relevant things bearing on whether the laboratory is being operated in compliance with national standards. Further, upon completion of the inspection, the inspector is to provide a preliminary report summarizing indications of violations, and, within 30 days of the completion of the inspection, a written final report of the findings is to be prepared and sent to the person in charge of the laboratory. Third, it is obvious that absent inspection, it would be impossible to determine whether the national standards truly were being met.

Obviously, the fourth consideration—history of extensive Federal or State regulation—is a test that cannot be met. However, it is not as if the field has long been an unregulated one since the state of the art is so new. In any event, the potentially hazardous conditions of employment in a recombinant DNA laboratory and the potential danger of recombinant DNA itself certainly justify warrantless administrative inspections in this case. See *Youghiogheny & Ohio Coal Co.* v. *Morton*, 364 F. Supp. 45 (S.D. Ohio, 1973) and *United States ex. rel. Terracizno* v. *Montanye*, 493 F. 2d 682 (2d Cir.), *cert. denied* 419 U.S. 475 (1974).

105(b). Samples

This subsection requires that any samples of recombinant DNA or related materials be provided at the request of an inspector, to determine if the requirements of sections 472, 474, and 475 are being complied with. In general, this section would be exercised only to independently test strains of plasmids, viruses, bacteria, or cell lines to make sure that they were not contaminated. It could, however, be used to test for certain requirements of biological containment, specified for certain recombinant DNA activities.

105(c). Detention of material

Inspectors may seize and impound any recombinant DNA or related material believed to present a significant risk to health or the environment. They may do this unilaterally at their own discretion. However, the period of detention may generally not exceed 20 days, although the Secretary may grant an additional ten day detention period if required to institute an action for seizure or destruction under section 104(b). Such material may be moved from its place of detention only if released by the Secretary or the expiration of the applicable detention period, or, of course, as the result of a court order under section 104(b). Since such biological materials are generally perishable and frequently unstable, it is the intent of the committee that every effort should be made to store any such detained material in a way so as to preserve its chemical, biological, and physical properties to as great an extent as possible, until such time as the material is returned to its owner or original use, or permanently seized or destroyed under a court order.

105(d). Waiver of search warrants

No individual designated as an inspector is required to obtain a search warrant before entering any facility, conveyance or real property. It is expected that inspections will be conducted in as non-destructive a way as possible with the cooperation of those involved with recombinant DNA activities. However, should an inspector be refused entry (an act prohibited by section 103(a)(3)(C)), a search warrant

is not required for an inspector to carry out his duties under this act,

105(e). Conflict of interest

This subsection prohibits the Secretary from designating an individual to conduct an inspection of a project involving a recombinant DNA activity in which that person is engaged or has a financial interest.

This provision is specifically applicable to members of a biohazards committee who may be engaged in a recombinant DNA activity. However, it does not prohibit such an individual from inspecting the laboratories or work of colleagues whose laboratories may be located at the same institution or company. It is designed only to avoid any conflict of interest in inspections authorized by and conducted under the provisions of this Act.

The term "financial interest" as used in this subsection means a situation where an individual may stand to profit financially from the success of a recombinant DNA activity, either because he has invested in a company conducting such an activity or because his employment or salary is dependent on the profits or financial gain from or funding of such an activity. Thus, a company stockholder could not be authorized to inspect that company's recombinant DNA activities, and a person being paid from a grant to support a recombinant DNA project could not be authorized to inspect anything relevant to that project. An employee of a company conducting recombinant DNA activities could act as an inspector only with respect to projects not supported by the company. If questions of doubt arise as to whether or not there is a conflict of interest, it is expected that inspections will be assigned to individuals for whom no such conflict could exist.

In the case of university faculty members or Government employees, the simple fact that an individual receives a salary from that university or Government agency which also pays the salaries of others conducting recombinant DNA activities, is not to be interpreted as a "financial interest" in a recombinant DNA activity, since, presumably, his salary would not depend upon the success of any recombinant DNA activity (other than his own, should he happen to be engaged in recombinant DNA work).

SECTION 106. EFFECT ON STATE AND LOCAL REQUIREMENTS

106(a) Federal preemption of State and local requirements

It is the intent of the committee that the recombinant DNA Act shoudl provide a uniform comprehensive set of safety regulations readily adaptable to all local situations where recombinant DNA activities are being conducted. Additional, more stringent or duplicate State or local regulations are, therefore, considered to be unnecessary. Subsection 106(a) states that any State or local requirements are, in effect, preempted by the Recombinant DNA Act.

However, the committee recognizes that it may be impossible to accurately anticipate or take into account in advance the nature of every situation which could arise involving recombinant DNA. Highly unusual situations or those affected by some unique local condition, would undoubtedly first come to the attention of those locally involved with the activity.

The committee also acknowledges that it is an important Constitutional prerogative for State and local governments to be able to deal legally with issues which are primarily local in nature, where Federal action would be inappropriate. It is to be noted, however, that local action is not always based upon a careful consideration or understanding of the available facts on a particular issue. It is thus the committee's intent that any additional or more stringent requirements which are to be imposed be truly justified on factual and rational grounds, and only because a convincing argument can be made that the Federal requirements provide inadequate protection of public health or the environment. That is, it is the Committee's view that responsible local action be permitted but that arbitrary or unjustified local legislation would not only be unnecessary, but might seriously impede the important freedom which should be afforded to scientific inquiry.

106(b) Procedure and criteria for allowing of State and local requirements

Subsection 106(b) sets forth the criteria whereby a State or local government may impose additional or more stringent requirements governing the conduct of recombinant DNA activities. Specifically, paragraph (1) precludes the possibility of a more lenient requirement from being imposed locally, and paragraph (2) states that the requirement must be shown to be necessary to protect health or the environment. It is this latter provision which is the basis for any State or local laws which will be permitted to override the Federal regulations.

The State or local government is required in subsection (b) to formally petition the Secretary for an exemption from subsection (a) for specific requirements, including the reasons why such requirements are indeed necessary to protect health or the environment. It follows that such a petition or application must include an argument that the Federal standards are not adequate to protect health or the environment, at least in the specific local circumstances under consideration.

The Secretary must grant an oral hearing to the petitioner, no later than 60 days from the date the application is submitted. The presiding officer, shall, upon the conclusion of the hearing make written recommendation to the Secretary respecting approval of the application.

106(c) The Secretary's decision on whether or not to permit State or local requirements

In making his decision whether to approve or to disapprove the application, the Secretary must take into account any local conditions which would significantly alter the effectiveness of the Federal requirements. That is, the arguments of the State or local government regarding the adequacy of the Federal standards must be viewed specifically in the context of the local situation in which they are to be applied, unless it is the petitioner's intent to show that there is some general deficiency in the Federal requirements. In the latter case, if the Secretary finds that a general inadequancy of the Federal requirements has been demonstrated, he should take measures to amend the Federal standards to correct the deficiency.

If the Secretary determines that a State or local government has shown that an additional or more stringent requirement is necessary,

then he is bound by law to grant an exemption from subsection (a) for these specific provisions. That is, the Secretary has discretionary powers in making the judgment as to whether or not a proposed requirement is necessary to protect health or the environment, and this decision should be based upon the best available scientific and risk assessment data. However, if he should decide that a State or local government has proven its case, then he shall grant an exemption to the provision that the Federal requirements supercede all State and local requirements. It is the committee's intent that all such decisions be based purely upon health and safety considerations and, thus, there should be no discretionary powers granted to the Secretary where a decision could be made upon other, less relevant grounds.

The Secretary must approve or disapprove the application within either 60 days from the conclusion of the hearing or one hundred twenty days from the date of the application, whichever occurs later. The Secretary's decision shall be in writing, contain the presiding officer's recommendation if a hearing was held, and shall include a complete discussion of the reasons for the decision.

SECTION 107 TRAINING AND STUDIES

107(a) Training courses in the safe handling of recombinant DNA

The Secretary is authorized to conduct and support training courses and workshops to instruct personnel to be engaged in recombinant DNA activities in any relevant safety procedure or technique. Such courses might be set up under the auspices of the National Institutes of Health or the Center for Disease Control, for example. The Secretary may also provide grants to institutions or to local biohazards committees to set up and conduct training programs where justified by local needs.

The committee believes that the proper training of personnel is essential to the success and effectiveness of the Recombinant DNA Act. It is, therefore, expected that the Secretary will give the training of personnel high priority in administering the provisions of this Act.

107(b) Risk assessment studies

The Secretary is required to conduct and support "on a continuing basis" studies designed to evaluate the risks to health and the environment which may be presented by recombinant DNA activities. This should include the financial support of specific experiments designed to evaluate hazards, such as that being planned at the National Institutes of Health by Drs. Malcolm Martin and Wallace Rowe to assess the probability of transferring tumor virus genes to mice via *E. coli* K–12, as well as risk assessment workshops such as that held in Falmouth, Mass., on June 21–22, 1977. Such studies and programs are essential in making sure that the safety regulations contained within the Recombinant DNA Act accurately reflect the best possible evaluation of the actual risks posed by any particular recombinant DNA activity. It is wasteful and burdensome to the investigator and the Government to continue in effect requirements which have been shown to be overly stringent to provide adequate protection of health and the environment for a specific recombinant

DNA activity. Similarly, a standard should not remain in effect which is too lenient, simply because of a lack of information concerning potential hazards.

In order to assess the limits of the actual risks posed by recombinant DNA activities, the Secretary is encouraged by the Committee to permit exemptions (as authorized under paragraph (1)) from sections II and III of the NIH Guidelines, including the list of prohibited experiments, and conduct, under very high physical containment if necessary (P–4, or P–3 if judged to be of lower risk), experiments designed to elicit the worst-case scenarios which are the basis for much of the stringency in the current NIH Guidelines. That is, using an appropriate animal system, it would be desirable to determine just to what extent pathogenic strains of *E. Coli* or other organisms capable of accepting *E. coli* plasmids could be made *more* pathogenic by the deliberate addition of a variety of recombinant DNA's. Similar experiments should be done with modified animal and plant viruses, as should experiments to test the persistence of organisms containing recombinant DNA in competition with natural organisms in a variety of ecological settings.

Such studies, many of which are now prohibited under the NIH Guidelines, would be of immense value in bringing into perspective just how great the potential hazards from recombinant DNA work may be and how probable the occurrence of an untoward event may be.

SECTION 108 RELATIONSHIP TO OTHER FEDERAL LAWS

108(a) Regulation of recombinant DNA activities under other Federal laws

The Recombinant DNA Act does not abridge the authority of any Executive Agency to regulate recombinant DNA activities under any other statute. It is the committee's intent that the Department of Health, Education, and Welfare be the lead regulatory agency, and that there not be more than one set of requirements or regulations governing the same recombinant DNA activity. However, there are activities peripheral to the recombinant DNA activities covered by the Recombinant DNA Act, which other agencies would be expected to regulate, such as the purity of products manufactured by recombinant DNA techniques to be sold as drugs, biologicals or food, occupational safety in manufacturing plants, agricultural products of recombinant DNA containing organisms, or the transportation of potentially hazardous biological material.

108(b) Relationship to the Occupational Safety and Health Act of 1970

Neither the safety requirements specified in section 102(a) nor any personnel safety standards or requirements which the Secretary may prescribe under section 102(d) shall be considered to be exercising statutory authority under the Occupational Health and Safety Act. That is, the prescription and enforcement of occupational health and safety standards as required by the Occupational Health and Safety Act are in no way supplanted or superseded by any provision of the Recombinant DNA Act.

TITLE II—COMMISSION FOR THE STUDY OF RESEARCH AND TECHNOLOGY INVOLVING GENETIC MANIPULATION

SECTION 201 ESTABLISHMENT OF A STUDY COMMISSION

201(a) Establishment of a commission

This subsection establishes by a law, a commission to be called the Commission for the Study of Recombinant DNA Activities.

201(b) Membership and compensation of the commission

The Secretary of Health, Education, and Welfare is to appoint the 13 commissioners from individuals distinguished in the fields of medicine, law, ethics, theology, the biological, physical and environmental sciences, philosophy, humanities, health administration, Government, and public affairs. While not required to do so under this title, the committee encourages the Secretary to consider the recommendations of the National Academy of Sciences, the National Science Foundation, the Environmental Protection Agency, the National Institute of Occupational Safety and Health, public interest groups and other appropriate entities. Members are appointed for the life of the Commission (30 months) and should be appointed by the Secretary within a reasonable time after the date of enactment.

It is important that the membership reflect rather diverse backgrounds and expertise. It is not the committee's intent that a substantial fraction of the membership need ever to have been directly involved in recombinant DNA activities. The commission should include, however, a number of scientists who are fully familiar with the technical details of recombinant DNA methods (and other genetic manipulation techniques) as well as the NIH Guidelines. The committee also intends that the membership include distinguished individuals from a variety of scholarly disciplines and professions. Thus, the commission should have both the technical expertise necessary to evaluate the scientific aspects of genetic manipulation in detail, and the broader public perspective required to effectively carry out the studies assigned to it in section 202.

Except for full time Federal employees, Commissioners shall receive the daily equivalent of the basic pay in effect for Civil Service Grade GS–18, for each day they are engaged in the actual performance of the duties of the Commission. In general, this would not be expected to exceed 2 or 3 days per month, if that. Travel expenses are also provided, while in the performance of the duties of the Commission, including travel to and from Commission meetings.

201(c) Chairmanship of the Commission

The members of the Commission shall select a chairman from among the Commission membership.

201(d) Staff and Consultants for the Commission

The Commission has the authority to hire and determine the pay of such staff personnel at it considers desirable, subject to the provisions of title 5, United States Code, governing civil service appointments. It may also hire, on a temporary basis, experts and consultants as needed.

Since the Commissioners are expected to serve on a part-time basis, with major professional appointments elsewhere, staff personnel will be necessary to handle much of the routine functioning of the Commis-

sion, such as correspondence, etc., as well as gathering information and preliminary analysis of many of the issues.

It is likely that there will be times when the Commission will require very specific knowledge or analyses which are outside the expertise of any of the Commissioners of staff members. Thus, the use of technical experts and consultants would be expected to be essential to the proper functioning of the Commission.

SECTION 202. DUTIES OF THE COMMISSION

Paragraph (1) directs the Commission to conduct a study of Federal policy regarding activities regarding genetic manipulation or organisms and viruses including consideration of the interim controls described in title I of this act, the effect of non-Federal requirements and the need for Federal preemption, federally sponsored risk assessment studies and the progress of federally sponsored basic and applied research.

Paragraph (2) requires the Commission to assess the long term consequences of the development of a technology capable of the genetic modification of organisms and viruses, including the anticipated medical and commercial applications, and the ethical, moral, social, economic and political implications of the development and use of such technology.

SECTION 203. HEARING AUTHORITY, COOPERATION BY OTHER FEDERAL AGENCIES AND THE DISCLOSURE OF CONFIDENTIAL DATA

203(a). The Commission shall hold public hearings as appropriate to assist it in carrying out its functions under sections 202 and 203.

203(b). Cooperation by other Federal agencies

The Commission is empowered to secure information from any Federal agency to enable it to carry out its duties. The head of any such department or agency shall furnish such information upon request.

203(c). Disclosure of data

The disclosure of any confidential information obtained by the Commission is governed by section 480, of title I of the Recombinant DNA Act.

SECTION 204. COMMISSION REPORTS AND TERMINATION OF THE COMMISSION

204(a). Preliminary report

Within 18 months of the date of enactment, the Commission must report to Congress the preliminary results of the evaluation prescribed by paragraph (1) of section 202. This requirement is to assist Congress in determining whether or not to extend Title I of this Act beyond two years, and, if so, what changes might be needed.

205(b). Final report

The Commission must complete the studies prescribed by section 202 and, on the basis of its findings, make recommendations to the Con-

gress, the President and the appropriate Federal agencies regarding Federal action which the Commission determines should be taken to promote, regulate or study activities involving genetic manipulation. It is the committee's intent that the final report of the Commission be published and made available to the public.

204(c). Termination of the Commission

The Commission shall terminate within 60 days of the date upon which it has completed its studies and submits its final report to Congress, the President and the appropriate Federal agencies.

INFLATION IMPACT STATEMENT

The committee anticipates that the enactment of H.R. 11192 will have a negligible impact on inflation in the biomedical research area and in Federal spending. As determined by the Congressional Budget Office, the cost to the government of expanding the scope of the NIH Guidelines governing recombinant DNA activity to encompass all such activity regardless of its funding source would be less than $3 million annually. In view of the potential hazards to the public health and the environment from improperly conducted recombinant DNA activities and the potential benefits to society which may derive from such activities, the minimal increases in expenses which may accrue to entities engaged in recombinant DNA activities in connection with compliance with the requirements of the proposed legislation are wholly appropriate.

CONGRESSIONAL BUDGET OFFICE COST ESTIMATE

A cost estimate was requested on H.R. 11192 when it was ordered reported from the Committee on Interstate and Foreign Commerce, and the Congressional Budget Office has provided the following information.

CONGRESSIONAL BUDGET OFFICE,
U.S. CONGRESS,
Washington, D.C., March 23, 1978.

Hon. HARLEY O. STAGGERS,
Chairman, Committee on Interstate and Foreign Commerce,
U.S. House of Representatives,
Washington, D.C.

DEAR MR. CHAIRMAN: Pursuant to Section 403 of the Congressional Budget Act of 1974, the Congressional Budget Office has prepared the attached cost estimate for H.R. 11192, a bill to extend for two years the scope of the containment requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation.

Should the Committee so desire, we would be pleased to provide further details on the attached cost estimate.

Sincerely,

ALICE M. RIVLIN,
Director.

CONGRESSIONAL BUDGET OFFICE—COST ESTIMATE

MARCH 23, 1978.

1. Bill number H.R. 11192.
2. Bill title: None.
3. Bill status:

As ordered reported by the House Committee on Interstate and Foreign Commerce on March 14, 1978.

4. Bill purpose:

A bill to extend for two years the scope of the containment requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation.

5. Cost estimate:

Projected Costs

	Millions
Fiscal year 1979:	
Estimated authorization level	$2.42
Costs	2.23
Fiscal year 1980:	
Estimated autrorization level	3.00
Costs	2.95
Fiscal year 1981:	
Estimated authorization level	2.79
Costs	2.81
Fiscal year 1982:	
Estimated authorization level	2.15
Costs	2.20
Fiscal year 1983:	
Estimated authorization level	2.30
Costs	2.29

NOTE.—The costs of this bill fall within budget function 550.

6. Basis for estimate:

Enactment of H.R. 11192 would extend the National Institutes' of Health regulatory and experimental guidelines for recombinant DNA research to all public and private recombinant DNA activities. Currently, only those activities funded by the NIH are covered. The bill also authorizes the creation of a commission for the study of research and technology involving genetic manipulation.

The assumptions made in estimating the authorization levels of H.R. 11192 were:

Approximately 200 newly covered laboratories will require 50 new regulatory inspectors at an average wage of $20,700 plus 70 percent for employee benefits, travel costs, and administrative expenses (all inflated in outyears by CBO's federal wage deflator); and

Creation of the study commission for the full 32 months authorized will require 10 members from outside the NIH at the stipulated GS-18 wage rate; since there is no precedent for estimating periodic increases in salary at this level, no assumption for future salary adjustments were made; an additional 60 percent for travel and administrative costs was added and inflated in outyear by CBO's federal wage deflator.

It is assumed that the estimated authorization levels will be fully appropriated at the beginning of each fiscal year. The costs are estimated on the basis of a current year spendout rate of .92 and a prior year balance spendout rate of .08.

While H.R. 11192 also provides for the imposition of penalties on laboratories with violations, HEW estimates that few, if any, penalties will be assessed.

7. Estimate comparison: None.

8. Previous CBO estimate: None.

9. Estimate prepared by: John Nelson (225–7766).

10. Estimate approved by: James L. Blum, Assistant Director for Budget Analysis.

PROGRAM OVERSIGHT

The committee's principal oversight activities with respect to this program have been conducted by the Subcommittee on Health and the Environment in connection with its consideration of the legislative authorities for the program. Legislative hearings on the program were conducted in March of 1977 (Serial No. 95–18), and the findings are discussed in the report as the proposed legislation is designed to respond to the subcommittee's findings. The committee has not received oversight findings with respect to this program from its Subcommittee on Oversight and Investigations or from the Committee on Government Operations. Published hearings on the science policy implications of DNA recombinant molecule research were conducted by the Subcommittee on Science, Research and Technology of the Committee on Science and Technology in 1977 which were useful to the committee in its deliberations.

AGENCY REPORTS

Agency reports were requested on H.R. 4759, a similar predecessor to H.R. 11192, from the Office of Management and Budget and the Department of Health, Education, and Welfare, but to date no reports have been received.

DISSENTING VIEWS OF REPRESENTATIVES HENRY A. WAXMAN, BARBARA A. MIKULSKI, ANDREW MAGUIRE, EDWRD J. MARKEY, MARC L. MARKS, AND RICHARD L. OTTINGER.

We are extremely disappointed that H.R. 11192 makes virtually no provision for public participation in regulation of recombinant DNA research. The bill unnecessarily mandates Federal preemption of State and local regulation unless these governmental units can meet the heavy burden of proving the "necessity" of their own regulations. Almost total discretion is given to the Secretary of Health, Education, and Welfare to exempt DNA research from Federal regulation by order, without the benefit of any public rulemaking proceeding. Because of these defects in the bill, we must respectfully dissent from the report of the Committee.

I. ABSENCE OF STATUTORY REQUIREMENTS FOR PUBLIC PARTICIPATION

H.R. 11192 was introduced in the full Commerce Committee as a substitute for H.R. 7897, a bill reported by the Health and Environment Subcommittee after extensive hearings and Subcommittee deliberation. In H.R. 11192, a number of requirements for public participation which had been included in the Subcommittee's bill have been eliminated.

The subcommittee bill would have established by statute a "Recombinant DNA Advisory Committee" of 17 members, of whom at least nine were to be individuals not engaged in recombinant DNA research. Included in the tasks given to the Advisory Committee was the responsibility to advise the Secretary regarding the type of regulations promulgated under the Act. This Advisory Committee has been eliminated in H.R. 11192.

The subcommittee bill had also required establishment of a "Local Biohazards Committee" in each community where DNA research is to be conducted. Representatives of the public interest were specified by the Subcommittee bill to be members of such Committees. "Local Biohazards Committees" are not required by the language of H.R. 11192.

Section 102(d) of H.R. 11192 authorizes but does not require the Secretary to establish "local entities to assist in administration and enforcement" of the Federal regulations to be promulgated under section 102(a)(1).

It does not appear that these "local entities" will be anything more than institutional peer review committees, with corporations or educational institutions conducting DNA research in essence policing themselves. There is no requirement that representatives of local governments or citizen interest groups be made members of these "entities," nor is there any requirement that such representatives, if appointed, be given a vote in "entity" deliberations.

Section 105 of H.R. 11192 allows the Secretary to designate individuals to be inspectors for the purposes of enforcing the act's requirements. No standards for selecting such inspectors are stated, other than that an inspector must not be conducting or have a direct financial interest in DNA research. This section allows for the possibility that an employee of an institution conducting DNA research can be designated as an inspector of the research activity at that same institution. When coupled with the vague language regarding the local "entities" to be established, the resulting situation is that DNA research could be conducted without any public involvement in regulation and without any direct Federal safety review. The public health and the environment are not protected by this regulatory scheme, which allows private institutions to define the public interest.

The subcommittee bill provided in section 473(e) for citizen petitions to the Secretary to initiate rulemaking proceedings. This provision, which allowed the people to be involved in a significant way in HEW's regulatory activity, has been eliminated in H.R. 11192.

Section 201 of H.R. 11192 establishes a Commission for the Study of Research and Technology Involving Genetic Manipulation. Although this section includes a lengthy list of professions from which Commission members may be selected, there is no specific requirement for designation of members representing public interest or citizen groups. Total discretion is given to the Secretary, who could, if he so desired, appoint only scientists to the Commission. There is no restriction on the number of individuals involved in genetic research who may be appointed to the Commission.

The effect of the deletions and variations from the subcommittee bill, as well as the vague criteria for Commission membership, is that mandatory involvement of the citizenry in rulemaking, local enforcement, and study of research issues at the national level is absent from H.R. 11192.

In committee debate on this measure, proponents of H.R. 11192 offered virtually no rationale for the glaringly evident lack of provision for public participation.

In the committee's earlier debate on the Subcommittee bill, only limited opposition had been raised to the public involvement requirements eliminated in H.R. 11192. Opponents of these requirements expressed the view that even limited citizen involvement in regulation might be inappropriate when related to research activity, particularly if such involvement resulted in placing limits on that research.

We totally reject the view that the people are incapable or unworthy of conducting public business, and that only a regulatory or research elite can make reasoned decisions on the complex regulatory issues of the day.

H.R. 11192 as reported by the committee essentially leaves all regulation of DNA research activity in the hands of the corporations and universities undertaking such research, and in the hands of HEW's National Institutes of Health (NIH), the chief Federal advocate for such research.

NIH is the Federal government's primary biomedical funding agency. In this position, it plays what can be described as a "promotional" role in the research community. H.R. 11192 places NIH, through the Secretary, in the position of being both promoter and

regulator, a situation similar to that of the now-defunct Atomic Energy Commission. There is an obvious conflict of interest inherent in this situation.

In a democratic society, representatives of the citizenry should be involved in making decisions about activities of major importance in their communities. A clear call for such involvement will not be found in the language of this bill.

The absence of such provisions is totally contrary to the great strides made by the Congress in recent years in mandating citizen participation, through designated representatives, in decisions that affect the lives of the people.

II. FEDERAL PREEMPTION OF STATE AND LOCAL REGULATION

H.R. 11192 provides that States and localities may not regulate DNA research activity within their jurisdictions unless their requirements and their requirements are "necessary" to protect health or the environment. The argument made by proponents of this section is that it provides for national uniformity of regulation and gives the correct role to an asserted Federal expertise. Proponents of this section also argue that without such a restriction, communities might attempt to "stop research" unthinkingly.

We must disagree with these assertions.

Section 102(b) of H.R. 11192, which allows the Secretary by order to exempt any DNA research activity from HEW regulations, itself allows for inconsistent regulation. In any case, it is not at all clear that a State or city should not be allowed to regulate to protect public health and the environment because its manner of regulation might be inconsistent with that of another governmental body. Indeed, on the day following committee action on this bill, the Commerce Committee reported out H.R. 10909, the Clinical Laboratory Improvement Act, which allows States to continue to regulate laboratory activities if their standards are at least as stringent as Federal guidelines. No additional requirement that any added regulations be found "necessary" by the Secretary is imposed by that bill. The pattern found in the Clinical Laboratory Improvement Act is the norm for health-related legislation: States and/or communities are free to regulate within their borders as long as they meet Federal minimum standards. Such a regulatory scheme allows for the utilization of Federal expertise, but also gives the people the most directly affected by a given situation the ability to impose additional requirements they reasonably believe are required to adequately protect the welfare of their communities.

The experience of Cambridge, Mass., where the type of local regulation was a topic of communitywide debate, has shown that local Government can and should be allowed to regulate in this research area. The outcome was a regulatory scheme that citizen and scientist alike can support. Neither the City Council of Cambridge nor the Maryland State Legislature, which has also acted in this area, "stopped research" by imposing their regulations. They did, however, exercise the powers which we allocate as a matter of fundamental principle to representative government in our society.

We attempted in Committee to effectuate our view that State and local governments should have the right to impose their own regulation

of research through support of two amendments to Section 106 of H.R. 1192. The first of these amendments, offered by Representaitve Mikulski, would have placed the burden on the Secretary to show that the local or State regulation was not necessary to protect public health or the environment.

The second amendment, offered by Representative Marks, would have changed the burden in section 106(b)(2) from a showing by local governments that their regulation is "necessary" to a more easily met showing that local regulation was "reasonable" to protect public health and the environment. Although the supporters of the H.R. 11192 substitute argued that this bill does allow for local regulation if such regulation is "reasonable," they steadfastly refused to support an amendment to say what they claimed they meant.

While we are greatly concerned that the protections afforded our people in this bill will in future years prove to have been insufficient for their protection, our fundamental concern as to the preemption issue is with the notion that a scientific elite and an insular Federal bureaucracy know what is best for the people—and that they, and not the people, directly or through their representatives, must be allowed to govern. That is the premise on which the preemption section in H.R. 11192 was drafted.

This attitude, which characterized much of the debate on this section, is contrary to the principles of Jeffersonian democracy, to our populist tradition, to our view of this nation as one of self-governing people.

III. DISCRETION IN THE HEW SECRETARY TO EXEMPT BY ORDER RECOMBINANT DNA ACTIVITIES

Sec. 102(b) of H.R. 11192 allows the Secretary of Health, Education, and Welfare to exempt by order any recombinant DNA activity which the Secretary finds does not present "a significant risk" if excused from the safety requirements of the NIH guidelines. This constitutes a significant change from the bill reported out of the House Subcommittee on Health and the Environment H.R. 7897. The subcommittee, after hearing testimony, researching this subject and deliberating for months, concluded such an exemption should be permitted only by regulation.

Debate by the full Interstate and Foreign Commerce Committee on H.R. 11192 disclosed that this sweeping exemption power was sought so that the Secretary of HEW could exempt risk assessment studies, among others, from the NIH guidelines. We think this poses serious potential risks for public health and the environment.

Permitting exemptions by order, instead of administrative regulation, eliminates any public comment. Thus, the last vestige of public participation in regulation of recombinant DNA is stricken from the legislation reported to full committee by the House Subcommittee on Health and the Environment. The Subcommittee bill, H.R. 7897, mandated that persons not involved in recombinant DNA activities and persons representing the public interest be members of the Recombinant DNA Advisory Committee and the Local Biohazards Committee. H.R. 11192 eliminates both these committees, as well as administrative hearings on exemptions from the NIH guidelines.

The authority conferred on the H.E.W. Secretary by H.R. 11192, by use of the word "significant", allows him to exempt activities

which are admittedly a hazard, but which, in the opinion of the Secretary alone, do not pose a "significant" risk.

We respectfully suggest that H.R. 11192 delegates unfettered discretion to the Secretary of H.E.W. without adequate standards to protect public health and the environment. Specifically, we think the broad exemption power is not sensible public policy for the following reasons:

1. Conflict of interest may result in a biased judgment on what constitutes a "significant risk"

Decisions involving recombinant DNA are made by the National Institutes of Health, which is the primary funding agency for recombinant DNA research. NIH awards grants and contracts in this field with the expectation that the United States will advance competitively with other nations in this rapidly developing field. There is an inherent conflict of interest when one involves the same agency in both financial subsidies and regulatory decisions. NIH, we think, will have a tendency to advise the Secretary of H.E.W. that research proposals seeking exemption from the NIH guidelines do not pose a "significant" risk.

2. The Secretary's broad exemption power will encourage requests for exemptions

Because H.R. 11192 provides no specific standards qualifying an experiment for an exemption, the Secretary of HEW may be inundated with requests for relief from the NIH guidelines. Indeed, applying for an exemption may become routine whenever a facility begins a new recombinant DNA experiment, or a new stage of an ongoing experiment. The result will be case by case decisions by the Secretary of HEW allowing exemptions. We do not think that such close involvement of the Secretary was ever intended by the Interstate and Foreign Commerce Committee. Nor do we think the scientific community wants the HEW Secretary a participant in day to day research decisions.

3. The Secretary's broad exemption power invites litigation by citizen groups

In debate by the full Interstate and Foreign Commerce Committee, it was said that the Secretary of H.E.W. should be able to exempt experiments by order from the NIH guidelines to save time. It is true that issuing an order is an expedited procedure less time consuming than the issuance of regulations, which require publication and comment. However, the exercise of the Secretary's exemption power without any limits in the law to restrain its arbitrary use will invite time-consuming litigation. Since all public representation is eliminated by H.R. 11192, the only way citizens can "participate" in regulation of recombinant DNA activities is through litigation. It is quite likely that concerned citizens who have not been allowed to comment on the appropriateness of an exemption will test the Secretary's order in court. They may seek temporary restraining orders or other forms of injunctive relief. Courts of equity, which can grant such relief, traditionally refuse to take jurisdiction of cases involving them in remedies requiring continuous and detailed court supervision. The courts will be reluctant to involve themselves in case by case decisions on recombinant DNA experiments.

4. Broad exemptions defeat the regulatory purpose of recombinant DNA legislation

When the Interstate and Foreign Commerce Committee debated the issue of federal pre-emption of State and local statutes, the prevailing view was that a uniform standard should apply to all recombinant DNA research, unless local or State regulations were necessary to protect health or the environment.

Clearly, granting power to the Secretary of HEW to exempt at will and by order any recombinant DNA research activities from the NIH safety guidelines defeats the goal of a uniform standard. It will create pockets of unregulated activities at research facilities across the country.

5. Deregulation of some experiments and not others by order of the H.E.W. Secretary will invite litigation by scientists

H.R. 11192 specifies no standards by which the Secretary can find that an experiment poses no "significant risk". Deregulation of some experiments and not others will give certain researchers a competitive advantage over others. Institutions excused from the guidelines may be able to perform their experiments more quickly and at less cost. Fierce competition to find constructive commercial applications for recombinant DNA, as well as the current race to win a Nobel prize, will lead scientists to test the Secretary's exemption orders in the courts. Manufacturers may assert legal claims that since exemptions are created by order rather than by regulations on which they can comment, exemptions granted to their competitors deny plaintiffs due process or equal protection. Manufacturers are sure to object if some of their competitors are relieved by the HEW Secretary from batch size limitations now imposed by the NIH guidelines.

6. Broad exemptions for recombinant DNA experiments make the NIH guidelines more difficult to enforce

Exemptions permitted by the Secretary of HEW will erode compliance with the NIH guidelines even in institutions which did not seek or were not granted exemptions. If it is known the Secretary exempted a certain type of experiment, scientists may see little reason to comply with safety guidelines if they are engaged in similar work. They will reason that the Secretary's order indicates non-observance of certain guidelines does not pose a "significant" risk. A Secretary's public order exempting a particular type of experiment from the NIH guidelines may be used in litigation to estop him from enforcing that guideline in any other research facility engaged in similar work. We feel that institutions not having an exemption will attempt to catch up with their competitors by disregarding the guidelines.

7. The Secretary's exemption power may expose laboratory workers to unknown risks

H.R. 11192 grants the HEW Secretary a general power to exempt experiments from the NIH guidelines without designating in regard to whom a "significant risk" should be evaluated. The Secretary might find that containment at a laboratory is sufficient enough that no "significant risk" is posed for the surrounding community. However, there is nothing in the law which addresses the significant risk which may be created for laboratory workers or graduate students engaged in recombinant DNA experiments.

H.R. 11192 does not mandate that the Secretary of HEW promulgate regulations to protect the safety of laboratory workers. The bill is silent on this issue. H.R. 7897, by contrast, did require the Secretary to issue regulations to protect the safety of laboratory workers. Compliance with such regulations was made a pre-condition to obtaining a license to conduct recombinant DNA research.

Recombinant DNA experimentation, just like research on radioactive isotopes, has potential benefits, and many unknown risks. Those who must work in recombinant DNA facilities to make a living deserve protection from potential hazards.

According to testimony at the DNA hearings held in 1977 by the House Subcommittee on Health and the Environment, both the National Institute for Occupational Safety and Health and the Labor Department have informed Dr. Frederickson at NIH that the NIH guidelines have not adequately addressed the occupational safety and health issues raised by recombinant DNA experimentation.

Many workers involved in recombinant DNA experiments at the present time have no statutory protection. The Occupational Safety and Health Act does not cover work by individual scientists, or research conducted at many public universities. State, county and municipal employees are not presently covered by the Federal occupational health and safety program.

Many students and employees at recombinant DNA laboratories are nonunion, or they may belong to separate unions. Without uniform union representation, it will be difficult for employees to enforce safe working conditions. H.R. 11192 eliminates protective provisions in H.R. 7897 which allowed an employee to report violations of the NIH guidelines by his employer with impunity. Under H.R. 11192 an employee risks being fired or demoted for reporting violations of the NIH guidelines. This makes H.R. 11192 once enacted even more difficult to enforce.

Dr. John F. Finklea, when he was still Director of NIOSH, gave excellent testimony at the DNA hearings held by the House Subcommittee on Health and the Environment in 1977 on potential hazards to lab workers conducting DNA experiments. NIOSH determines what physical and chemical hazards are present in the workplace, what adverse effects they produce, and how workers are best protected from such effects.

Dr. Finklea suggested that the potential risks to recombitant DNA workers were substantial enough that an effective medical surveillance system should be created. He wanted records of exposure kept, so that any outbreak of disease among recombinant DNA workers could be well monitored. It is believed that chronic disease patterns might occur in such workers many years later, and that this should be monitored by the Federal Government or the employer.

Based on Dr. Finklea's testimony, we believe the protection of students and workers engaged in recombinant DNA is an urgent need which should be addressed by any federal legislation on this subject. We quote key passages in Dr. Finklea's testimony to justify our concern:

> "We have found that private industries, including some of these corporations conducting or planning recombinant DNA research, have not always voluntarily and quickly dealt with

> other occupational safety and health problems. For example, one corporation contacted assured NIOSH that medical records for recombinant DNA research workers would be made available and therefore no central registry of such workers was necessary. This corporation at the same time took legal action disputing our authority for access to employment and mental records necessary to evaluate health risks at a plant with an apparent increase in cancer among the workers. This cancer had been reported to Federal authorities by workers in that plant." [1]

Later Dr. Finklea testified that such disregard for worker safety was not an isolated incident:

> We have had communications that suggest that research laboratories do not provide for adequate control for a number of regulated or suspected carcinogens. State officials and our own Institute have pointed out that teaching laboratories in our educational institutions have not done all that is necessary to prevent exposures to potentially harmful chemicals....
>
> In general, occupational safety and health programs among universities do not seem as well developed as those in industry....
>
> If there should be significant risks to health arising from recombinant DNA research, we could become aware of such hazards in several ways. Isolated cases or an outbreak of clinical illness among workers or in the community might be the first indicator....
>
> The present reporting system for laboratories is entirely voluntary. Isolated cases and even fatalities associated with laboratory exposures to infectious diseases are from time to time reported....
>
> The present voluntary reporting system would probably not be adequate to detect a subtle increase in infectious disorders that are frequent, not particularly severe, or not easily associated with the infectious agent being investigated in the laboratory.[2]

Those of us who dissent from the Interstate and Foreign Commerce Committee Report respectfully submit that recombinant DNA organisms may prove, like chemical carcinogens, radioactive substances, and slow viruses, to have the capability to increase the risk of disease many years after exposure. There is no way to prove what this risk may be at the present time. Clearly, DNA legislation should protect laboratory workers from the potential risks of such exposure. The protection they could have under NIH safety guidelines should not be arbitrarily removed when the Secretary of HEW issues an order exempting certain experiments from the NIH guidelines.

In summary, those of us who dissent from the Committee Report do so in the belief that the unknown risks of recombinant DNA

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[1] Recombinant DNA Research Act of 1977. Hearings before the Subcommittee on Health and the Environment of the Committee on Interstate and Foreign Commerce, House of Representatives, 95th Congress, First Session, March 15, 16, and 17, 1977, p. 290–291.
[2] *Id.* at 291–92.

research have never been adequately assessed. It is prudent, we believe, to proceed with constructive applications of recombinant DNA research only when adequate safeguards are provided for. Having heard the testimony at the hearings on DNA, and having studied this issue for almost a year, we believe the exemption provisions of H.R. 11192 do not offer the full protection our environment and public health require in a brave new world where corporations can now patent new forms of life.

The attached dissenting views are respectfully submitted to the Committee Report on Recombinant DNA by the following members of the Interstate and Foreign Commerce Committee who voted against reporting H.R. 11192 to the floor of the House:

HENRY A. WAXMAN.
BARBARA A. MIKULSKI.
ANDREW MAGUIRE.
EDWARD J. MARKEY.
MARC L. MARKS.
RICHARD L. OTTINGER.

SEPARATE VIEWS ON H.R. 11192, RECOMBINANT DNA RESEARCH ACT BY HONORABLE JAMES M. COLLINS (TEX.)

I recognize that within the scientific community there is a consensus that H.R. 11192, the Recombinant DNA Act, represents a reasonable interim measure of governmental control over activities which are perceived to be fraught with the prospect of much benefit and slight risk. At the same time, the endorsement of others who view legislation from the narrow perspective of its effect on scientific research cannot deflect proper scrutiny of certain unfavorable aspects of this legislation. I shall endeavor to highlight briefly a few of my concerns respecting H.R. 11192.

Section 105(d) of the bill attempts to authorize designees of the Secretary of HEW to conduct an inspection without obtaining a warrant from a neutral and detached judicial officer. I believe that such a warrantless administrative search is in harmony with neither the essence of the Fourth Amendment nor a series of relevant Supreme Court decisions. In light of the flexible probable cause standard for an administrative search, together with the fact that a warrant proceeding is an ex parte one, it is difficult to conceive of why warrantless searches should be permitted as a matter of course.

This bill stands for the proposition that government may regulate private research even when no Federal monies are involved. An aspect of this that is particularly worrisome is that with respect to certain noncommercial activities not involving government money which would not be protected by exemption from the Freedom of Information Act.

Upon considered reflection, I believe that it was undesirable to effectively preempt, in section 106, local and State requirements over DNA activities merely because certain scientists fear the consequences flowing from possible judgments exercised by duly elected non-Federal officials.

This interim bill, with its inevitable red tape and HEW bureaucracy that it will spawn, is likely an unwelcome harbinger of future increased Federal regulation in this field.

Though, as stated in the findings of the bill, "no hazard has been demonstrated," the Federal Government is unjustifiably moving into this area.

JAMES M. COLLINS,
Member of Congress (Texas).

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON THE RECOMBINANT DNA ACT

BEFORE THE

SUBCOMMITTEE ON SCIENCE, RESEARCH, AND TECHNOLOGY

HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

APRIL 11, 1978

Mr. Chairman and Members of the Subcommittee:

I am pleased to appear before this Subcommittee today to testify on behalf of the Department on the Recombinant DNA Act (H.R. 11192) as reported by the Committee on Interstate and Foreign Commerce. Mr. Chairman, the Department favors enactment of H.R. 11192 because this measure offers the most promising solution available for establishing national standards for the use of recombinant DNA techniques. Congressman Harley Staggers, Chairman of the Interstate and Foreign Commerce Committee, and Congressman Paul Rogers, Chairman of the Subcommittee on Health and the Environment, are to be commended for working effectively to develop an interim, two-year bill that provides for sensible regulation and public oversight. Your Subcommittee, Mr. Thornton, has also done an outstanding public service in the care and deliberation provided this most important research area in your extensive hearings over the past two years. H.R. 11192 reflects new scientific information and administrative developments since the release of the NIH Guidelines in June 1976 as do the revisions to the Guidelines proposed to me in September 1977 by the Recombinant DNA Molecule Program Advisory Committee (RAC). Let me review for you the scientific and administrative developments reflected in the bill and in the proposed revisions to the Guidelines.

Flexible Regulations

H.R. 11192 provides the HEW Secretary with a great deal of flexibility in implementing interim regulations. As you are aware, Mr. Chairman, the Report on the Science Policy Implications of DNA Recombinant Molecule Research by the Science, Research, and Technology Subcommittee supports this position. We believe it essential that the scope and mandate for regulation are based on clear scientific evidence of the safety or risks of this research. New scientific information on the safety of E. coli K-12 (the principal organism used in these experiments) indicates that extensive regulation in this research area is unwarranted. The report of the Commerce Committee accompanying H.R. 11192 and the report of your Subcommittee cite this evidence. Indeed, additional evidence suggests that recombinant DNA research in the laboratory may be very similar to events which occur in nature. If such evidence continues to accumulate, then the concern about creating new forms of life will be put into a new perspective.

At a public hearing on the proposed revisions to the Guidelines held by the Advisory Committee to the Director (DAC), NIH, on December 15-16, 1977, there was support for flexibility in the administration of the NIH Guidelines. There was strong support for a provision that would allow the Director, NIH, on the recommendation of the Recombinant DNA Molecule Program Advisory Committee (RAC) to exempt risk assessment experiments from the requirements of the Guidelines. There was general agreement that risk assessment experiments are essential to determine

what hazards, if any, exist. The report of your Subcommittee cites this same need. Thus, we strongly endorse the authority in H.R. 11192 for exemptions to permit risk assessment projects, and for projects where there is no significant risk to health or the environment. In sum, developing scientific information on the risks or lack thereof in this research requires flexibility in regulation. H.R. 11192 and the proposed revisions of the NIH Guidelines provide this flexibility.

Preemption

Under the current NIH Guidelines an administrative framework sets out the respective responsibilities of the local institution and the National Institutes of Health (NIH). Over the past year and a half, the implementation of the Guidelines by participants in this research has proceeded well. Some experiments have had to be postponed and some scientific work delayed by the presence of the Guidelines and their implementation. But the spirit of cooperation between NIH and local institutions has remained good.

The role for NIH has been to develop the standards and for the local institutions through their institutional biohazard committees (IBC) to review the research and monitor the activities in the laboratory. Please note that as part of the revision process we are considering substituting the term "Biosafety committee" for the term "Biohazard committee" throughout the Guidelines. But for the present, I will continue to use the term Institutional Biohazard Committee.

NIH has also reviewed actions by the institutional biohazard committees to ensure that the research protocols comply with the requirements of the NIH Guidelines. In the report accompanying H.R. 11192, the general administrative structure of the Guidelines is endorsed for purposes of regulation under the Act. Indeed, the Commerce Committee report encourages the Secretary to place most of the authority for local administration of the Act in the institutional biohazard committees.

We are considering, in the proposed revisions of the Guidelines, further responsibilities for the biohazard committees. In our view, it is essential that the responsibility for primary oversight lie with these committees rather than at the Federal level. These local institutional responsibilities must be increased in view of the impossibility of a sufficient Federal police force to enforce standards externally. A corollary, however, is the need for a common set of Federal standards. In its March 1977 report, the Interagency Committee on Recombinant DNA Research recommended preemption to ensure a single set of national standards. As the Interagency Committee pointed out, the potential hazards, if ever posed, would conceivably extend beyond the local to the national and international levels.

It is for this reason that we strongly favor preemption. It is the Administration's view that a standard of reasonableness, as determined by the Secretary, rather than necessity as in H.R. 11192, should apply when state or local governments petition to have their requirements govern. I would like to point out, Mr. Chairman, that the NIH Guidelines provide for strict standards to govern this research,

and in no sense can they be considered minimum national standards. Thus I believe, Mr. Chairman, that state and local governments will recognize the prudence and conservatism of these standards and find them to be a high standard for the protection of health and the local environment.

Public Participation

Your report and the Commerce Committee report state that public participation is essential. We wholeheartedly agree. We have tried to provide opportunities for public participation and comment in all phases of the development of NIH policies in this area. The current Guidelines were developed with extensive opportunity for public comment and review and, in large part, reflect suggestions from public commentators. All meetings of the Recombinant Advisory Committee are announced in the Federal Register and are open to public scrutiny. The original Guidelines and the currently proposed revisions have been reviewed at public hearings of the DAC. The membership of the DAC, in both instances, was augmented to assure that sufficient expertise and diverse opinions were present on relevant scientific, environmental, occupational, and public policy issues. At the most recent hearing, witnesses representing industrial and academic research and labor and environmental groups were invited to give testimony. In addition to the invited witnesses, a number of others were given an opportunity to testify.

We have encouraged public participation not only at the national level but at the local level. Recommendations for diverse membership on

the local biohazard committees are included in the present Guidelines. I am considering further mandates for public representation on those committees as they assume increased responsibilities for monitoring and oversight.

The study commission proposed in H.R. 11192, which has a mandate similar to that of the commission proposed in your report, would provide yet another focus for public participation at the national level. I endorse the concept of a study commission with broad membership.

Revisions and Implementation under the Legislation

We have completed a review of all the issues raised at the public hearing and in correspondence received before and after the hearing on the proposed revisions to the NIH Guidelines. We are now in the process of developing a decision document and an environmental impact assessment for the proposed revisions. The revisions under consideration include possible exemptions to the Guidelines and the administration of the Guidelines at the national and local levels, especially as they relate to public participation and review.

We have recently issued a decision that recombinant DNA research inventions developed under DHEW support may be patented by universities provided licensees adhere to the safety standards of the NIH Guidelines. We are currently considering inserting appropriate language in the Guidelines that will provide protection for proprietary and patent information, but will not compromise public disclosure of information on potential risks to health or the environment. The Commerce Committee report specifically

states that the Department should include in the regulations implementing H.R. 11192 provisions for the protection of proprietary data.

NIH filed an environmental impact statement on the recombinant DNA Guidelines in October 1977, and we are conducting an assessment of the environmental impact, if any, of the proposed revisions. Mr. Chairman, the National Environmental Policy Act (NEPA) requires that for "major federal actions significantly affecting the quality of the human environment" a detailed statement by the responsible official must be made. It should be noted that in the Commerce Committee's report it is stated:

> "It is the [Commerce] Committee's understanding that the Secretary will complete and file an EIS on all guidelines and regulations, as expeditiously as practicable, even after promulgation of the administrative regulations...."*

Under NEPA's requirements, it is more precise to say, Mr. Chairman, that the Department will conduct an assessment of the environmental impact of the standards and regulations. And based on the assessment document, a determination will be made on whether an EIS is specifically required.

Presently, we are moving as rapidly as possible to develop a decision document and an environmental impact assessment of the proposed revisions in order to put them into effect as rapidly as possible--in accordance with the Administrative Procedures Act--so that we can avoid unnecessarily heavy regulatory burdens--such as those in the current Guidelines.

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*Page 20 of Report 95-1005, the Report by the Committee on Interstate and Foreign Commerce accompanying H.R. 11192.

In light of our experiences in developing and implementing the NIH Guidelines, we believe that enactment of H.R. 11192 with our suggested changes will enable the Department to proceed expeditiously and in a spirit of cooperation. The Interagency Committee has been an invaluable forum for developing coherent and coordinated policies through the representation of all the relevant research and regulatory agencies. It has played an effective role in ensuring a commonality of standards among the research agencies, for example, the National Science Foundation and the U.S. Department of Agriculture. The Interagency Committee, or a similar entity, should continue to provide such oversight for the development of Federal policies. Advisory committees, both technical and public, must be present within the Department. The Recombinant Advisory Committee, the scientific and technical committee responsible for developing the standards, will need to be continued in some fashion. A public advisory committee like the Advisory Committee to the Director, NIH, should continue to consider recommendations from the technical group. The study commission, as designated in H.R. 11192, clearly could play some role here as well.

Finally, regulatory responsibility will need to be defined. Testifying before the Subcommittee on Health and Scientific Research of the Senate Human Resources Committee, April 6, 1977, Secretary Califano said:

"NIH [will] recommend the revisions in the guidelines, review and clarify the technical issues, and handle, if you will, the standard setting, the philosophy, the scientific input, and then turn over to CDC the functions of licensing facilities and maintaining the registry and operating and promulgating standards. Both organizations would obviously have to be involved in training workers and in working with those outside the Federal Establishment as well as inside that are involved in recombinant DNA research."*

Indeed NIH, for the past 18 months, has worked closely with the Center for Disease Control (CDC) concerning safety aspects of the Guidelines. For example, NIH, in conjunction with CDC, has been developing mechanisms for assisting institutions in managing possible laboratory emergencies and for providing direct assistance when appropriate. Also, NIH and CDC have been reviewing packaging and shipping requirements relevant to recombinant DNA activities. Further, NIH and CDC have collaborated closely in revising the CDC Classifications of Etiologic Agents on the Basis of Hazard. This classification scheme underpins some of the safety requirements of the Guidelines. Close coordination and consultation with the Food and Drug Administration and the Environmental Protection Agency will be essential since these agencies' regulatory authorities will come into play when recombinant DNA research inventions are ready for commercial development. The Occupational Safety and Health Administration will exercise its regulatory authority in the workplace.

*Page 92 of the published hearing record dated April 6, 1977, on the Recombinant DNA Regulation Act.

You and your Subcommittee are to be commended for your enormous efforts to educate the public and the scientific community in these matters.

In conclusion, I want to take this opportunity to thank you and the members of your Subcommittee for continuing interest in the development of recombinant DNA policies.

Thank you very much, Mr. Chairman.

95TH CONGRESS
2d Session
HOUSE OF REPRESENTATIVES
REPORT No. 95-1005, Part 2

RECOMBINANT DNA ACT

REPORT

BY THE

COMMITTEE ON SCIENCE AND TECHNOLOGY

together with

DISSENTING VIEWS AND INCLUDING A CONGRESSIONAL BUDGET OFFICE COST ESTIMATE

[To accompany H.R. 11192]

APRIL 21, 1978.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

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95TH CONGRESS } HOUSE OF REPRESENTATIVES { REPT. 95–
2d Session } { 1005 Part 2

RECOMBINANT DNA ACT

APRIL 21, 1978.—Ordered to be printed

Mr. TEAGUE, from the Committee on Science and Technology, submitted the following

REPORT

together with

DISSENTING VIEWS

[To accompany H.R. 11192]

[Including cost estimate of the Congressional Budget Office]

The Committee on Science and Technology, to whom was referred the bill (H.R. 11192) to extend for 2 years the scope of the containment requirements and the requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation, having considered the same, report favorably thereon with amendments and recommend that the bill as amended do pass.

The amendments are as follows (page and line references are to the bill as reported by the Committee on Science and Technology):

Page 2, line 17, strike out "is" and insert in lieu thereof "may be".

Page 7, line 7, strike out "may" and insert in lieu thereof "shall".

Page 7, line 10, after "(a)(1)" insert the following:

> , as well as provisions giving due consideration to the need for protection against improper or unwarranted disclosure of privileged, confidential, or proprietary information, trade secrets, and information held under patent rights

Page 8, line 22, strike out "shall" and insert in lieu thereof "may".

Page 17, lines 1 and 2, insert the following new subsection:

(c) No part of this title shall remain in effect beyond the end of the period specified in section 102(a)(1).

Page 17, line 6, after "established" insert ", within the Department of Health, Education, and Welfare,".

Page 17, lines 12 and 13, strike out "Secretary of Health, Education, and Welfare" and insert in lieu thereof "President".

Page 17, line 13, strike out "Secretary" and insert in lieu thereof "President".

Page 17, line 15, strike out "in the fields of" and insert in lieu thereof "in such fields as".

Page 19, line 16, strike "the risk to health and the environment" and insert in lieu thereof "such risks to health and the environment as may be".

Page 20, line 4, strike out "and" after the semicolon.

Page 20, line 6, after "economic," insert "environmental.".

Page 20, line 8, strike out "technology," and insert in lieu thereof the following:

> technology, as well as the significance of lessons learned through recombinant DNA research and its allied science policy issues; and

Page 20, lines 11 through 14, insert the following new subparagraph:

> (C) a comprehensive assessment of the status and applications, achieved or anticipated, of genetic manipulation technology in other nations engaged in such activities.

Page 20, line 25, strike out "Secretary" and insert in lieu thereof "Commission".

(Much of the factual information which follows is the same as that contained in Part I of this report, prepared by the Committee on Interstate and Foreign Commerce.)

PURPOSE OF LEGISLATION

The purpose of the legislation is to assure that all research and other activities involving recombinant DNA molecules are conducted in accordance with national safety standards designed to prevent the creation and escape of genetically modified organisms or viruses which could pose a threat to public health or the environment. At the same time, however, the use of recombinant DNA methods is recognized to be of exceptional value to science. Thus, an additional purpose of the legislation is to prevent the imposition of unnecessarily restrictive state and local requirements.

At present, work in this area supported or conducted by the National Institutes of Health must be carried out in accordance with safety guidelines prepared and released by NIH. Most other Federal agencies have adopted the NIH Guidelines as agency policy. However, some public and all private recombinant DNA activities are not bound to follow any set of safety precautions.

H.R. 11192 is a 2-year interim control bill which would:

(1) Require that the sections of the NIH Guidelines, as currently amended, on Contaminant (Section II) and Experimental Guidelines (Section III) apply to all parties conducting recombinant DNA activities;

(2) Empower the Secretary of Health, Education and Welfare to promulgate administrative regulations, revise the Guidelines to reflect new scientific data, and exempt from the Guidelines activities determined to present no significant risk to health or the environment or for specific risk assessment studies;

(3) Give inspection authority to the Secretary of HEW and empoyer him to enforce the Guidelines, as appropriate, by (a) suspension of research grant funds, (b) a civil penalty ($5,000) or (c) seeking an injunction through the courts;

(4) Preempt States or political subdivisions thereof from establishing or continuing in effect any requirement for the regulation of recombinant DNA activities. However, the Secretary would be authorized, upon application and after considering local conditions, to approve a State or local requirement if it is the same as, or more stringent than a Federal requirement and if the additional requirement is necessary to protect health or the environment; and

(5) Establishes a study commission to evaluate Federal policy on activities involving genetic manipulation as well as the long term applications of gene splicing technology.

The interim controls and the study commission are established for 2 years. The Committee anticipates that within 1 to 1½ years after enactment, the appropriate Congressional subcommittees would exercise their oversight responsibilities to assess the current need for uniform standards and the performance of DHEW in administering the NIH standards to all parties. Based upon the performance of the Department and the current state of the art, appropriate legislation will be developed as needed.

SUMMARY OF THE LEGISLATION

Scope of legislation

The safety standards cited in this act, as well as any administrative requirements or regulations promulgated by the Secretary, would cover any activities (including research, transportation or commercial activities) involving recombinant DNA molecules which are addressed in section III of the NIH Guidelines, unless specifically exempted under this act. They would, therefore, apply to all private and governmental entities engaged in such activities.

Only activities involving recombinant DNA molecules which are formed by joining DNA segments outside of living cells are included in Title I of this Act, which establishes interim regulation of recombinant DNA activities. However, the scope of the study commission as set forth in title II, includes all types of genetic manipulation.

This act expires 2 years from the date of enactment.

Administrative responsibility

The responsibility for implementing the Recombinant DNA Act would rest entirely with the Secretary of Health, Education, and Welfare. However, the legislation would not affect the authority of any other Federal agency which has jurisdiction over certain activities which are in some way relevant to recombinant DNA. Specifically, no portion of the Occupational Safety and Health Act would be superceded by the Recombinant DNA Act. Where appropriate, other Federal agencies would be expected to cooperate with DHEW in carrying out its responsibilities under this Act.

Extension of the Safety Requirements of the NIH Guidelines to All Public and Private Entities

The standards described in section II (Containment) and section III (experimental guidelines) of the current NIH Guidelines would apply to all public and private recombinant DNA activities. As section IV (roles and responsibilities) is intimately tied to the NIH granting process, it is inappropriate as a general provision. Thus, under the proposed legislation the Secretary of Health, Education and Welfare is to promulgate administrative regulations within 90 days of enactment, without regard to the provisions of the Administrative Procedures Act.

Registration of activities

The proposed legislation would require each individual or entity engaged in a recombinant DNA activity to report in writing to the Secretary of DHEW a description of such activity and assurances that he will comply with the requirements under the legislation in carrying out such activity.

Revisions and exemptions

Revisions in the requirements are to be accomplished by regulation, with a public comment period.

Exemptions may be granted by order of the Secretary, subject to any conditions he may prescribe, for activities determined to pose no significant risk to health or the environment, or for specific risk assessment studies supported by the Secretary.

Inspection and enforcement

The Secretary of HEW is given broad inspection authority to ensure that all recombinant DNA activities are conducted according to the NIH standards. He may delegate much of this responsibility to local (biohazard or biosafety) committees at his discretion.

The proposed legislation spells out what constitutes a "prohibited act" and allows the Secretary to suspend HEW grant funds for violations, to impose a civil fine of $5,000, or to seek an injunction in the courts to restrain or enjoin activities done in violation of the requirements. U.S. district courts shall have jurisdiction over civil actions, including those brought for the seizure or destruction of material involved in a violation of the law.

Effect on State and local requirements

Under the proposed legislation, a State or local government could enact stricter laws which would supersede the requirements of this Act if it can be shown that such action is necessary to protect health or the environment, taking into account local conditions. That is, a State or local government would have to demonstrate that the requirement under the proposed legislation provide inadequate protection of health or the environment in the context of a particular local situation.

Training and studies

The Secretary would be authorized to conduct and support training programs in safety techniques for persons engaged in recombinant DNA activities and required to conduct and support risk assessment studies.

Study Commission

A 13-member study commission would be established to evaluate Federal policy on Recombinant DNA activities and to investigate the long term applications of gene-splicing technology. The commission could consider all aspects of genetic manipulation rather than being limited to the narrow scope of recombinant DNA activities. The commission is to complete its studies in thirty months and recommend appropriate Federal action.

BACKGROUND

Committee on Interstate and Foreign Commerce

On January 19, 1977, Representative Ottinger submitted House Resolution 131 calling for the promulgation of regulations governing all recombinant DNA research by the Secretary of Health, Education and Welfare, under section 361 of the Public Health Service Act. On February 7, 1977, Representative Ottinger introduced H.R. 3191, the "DNA Research Act of 1977" and on February 16, 1977, Representatives Ottinger, Badillo, Bedell, Corrada, Dellums, Duncan, Edwards, Gilman, Howard, Hughes, Jeffords, Kostmayer, Leach, Lehman, Mikva, Moakley, Neal, Richmond, Roybal, Scheuer, Simon, Steers, Walgren, Waxman, and Burke introduced H.R. 3591 and H.R. 3592, both identical to H.R. 3191.

Representative Solarz introduced H.R. 4322, the "Commission on Genetic Research and Engineering Act of 1977", on March 1, 1977. Representatives Rogers, Maguire, Preyer, Scheuer, Waxman, Florio, Markey, Walgren, Carter and Madigan introduced H.R. 4759, the "Recombinant DNA Research Act of 1977", on March 9, 1977.

Hearings on these bills were held by the Subcommittee on Health and the Environment on March 15, 16 and 17, 1977. On April 6, 1977, the administration's proposal, the "Recombinant DNA Regulation Act", was introduced as H.R. 6158 by Representative Rogers by request. Subsequently, a Subcommittee Discussion Draft was prepared on the basis of a subcommittee markup session on May 2, 1977, introduced by Representative Rogers on May 24, 1977, as H.R. 7418, the "Recombinant DNA Act". As a result of markup sessions in June, 1977, the subcommittee ordered reported a clean bill, H.R. 7897, introduced on June 20 by Representatives Rogers, Preyer, Scheuer, Waxman, Florio, Maguire, Markley, Ottinger, Walgren, Carter, Madigan, and Skubitz.

The Committee on Interstate and Foreign Commerce considered H.R. 7897 in markup sessions in September and October, 1977, agreeing to several amendments. However, the markup of H.R. 7897 was never completed and the bill was not reported by the Committee.

Representative Staggers introduced H.R. 10453 on January 19, 1978. This bill was not considered further. On February 28, Representatives Staggers and Rogers introduced H.R. 11192, which was subsequently considered by the Committee on Interstate and Foreign Commerce. On March 15, 1978, H.R. 11192 was considered, amended and ordered reported by the committee by a vote of 17 for and 6 against.

Committee on Science and Technology

The Subcommittee on Science, Research and Technology of the Committee on Science and Technology held hearings on the Science

Policy Implications of DNA Recombinant Molecule Research on March 29, 30, 31; April 27, 28; May 3, 4, 5, 25, 26; September 7 and 8, 1977. These hearings were preceded by six years of committee involvement with issues related to genetic research and engineering, during which three reports on the subject were issued.

On May 3, 1977 Chairman Olin E. Teague requested sequential referral of whatever bill on the subject of recombinant DNA research might be reported from the Committee on Interstate and Foreign Commerce. He also requested that any bills on this subject which come to the House from the Senate be dually referred to this committee.

The reasons for these requests were as follows:

(1) Rule X, Cl. (1)(r) of the House of Representatives gives the Committee on Science and Technology specific jurisdiction of "scientific research and development." Cl. 2(b) and Cl. 3(f) give this committee general and special oversight of "all laws, programs and Government activities" involving research and development, other than military R. & D.

(2) Recombinant DNA research is basic research. It stretches across the entire spectrum of fundamental biological science—plant and animal as well as human—and is not merely biomedical research. Substantively, therefore, recombinant RNA research is very much a part of the committee's responsibility.

(3) A vital element of national science policy is at issue—freedom of scientific inquiry. National science policy lies within purview of the Committee on Science and Technology.

(4) As a further matter of science policy, the government's action with regard to restricting recombinant DNA research will become a precedent which, if not carefully monitored, could spread to other areas of research.

On March 24, 1978, H.R. 11192 was reported by the Committee on Interstate and Foreign Commerce and sequentially referred to the Committee on Science and Technology for a period ending not later than April 21, 1978, for consideration of such provisions as fall within the jurisdiction of the committee.

The Subcommittee on Science, Research and Technology held hearings on H.R. 11192 on April 11. The bill was reported by the subcommittee on April 13.

On April 18 the full Committee on Science and Technology considered and ordered reported the bill H.R. 11192 as amended in subcommittee by a vote of 24 ayes and 4 nays.

NEED FOR THE LEGISLATION

The Committee on Interstate and Foreign Commerce, in Part I of this report which accompanies H.R. 11192, presents a detailed explanation of the need for this legislation. The Committee on Science and Technology is not here attempting to duplicate that justification or, for that matter, necessarily agree with it.

As noted above the committee requested sequential referral because of its specific jurisdiction of "scientific research and development" and national science policy. Thus committee actions on the bill were limited

by jurisdictional considerations. Some Members of the committee believe that the case for need is not persuasive; some would prefer to see very different legislation, or none at all.

In its explanation of the need for this legislation the Committee on Interstate and Foreign Commerce states that:

> It is to be borne in mind, however, that legislation is not a direct response to perceived possible hazards but to the fact that the NIH Guidelines only apply to a fraction of the recombinant DNA activities being conducted. The NIH Guidelines are the primary response to potential hazards and, therefore, legislation is justified only to the extent that safety guidelines are necessary.

The committee highlights this statement to raise several important points. First of all, although referred to as "Guidelines," the NIH standards which govern the conduct of recombinant DNA research funded by the NIH and other Federal agencies have the force of regulations over federally funded researchers. Special conditions for the conduct of experiments are required, and it is asserted that noncompliance will result in the termination of funding of research grants and contracts.

The question then can be asked, is it sensible or fair to require compliance with a set of standards by some researchers in this area and not by all? It is the considered belief of most persons who have studied the matter that all should proceed under the same rules or the "guidelines" will be little more than a charade. The desire to assure that recombinant DNA research be carried on under uniform ground rules throughout the country also has to be balanced with the desire to give assurance to the American people that every effort and caution is being taken to protect the public health.

The question of "how best do you enforce a common set of standards in this rapidly moving area?" remains to be answered. It may be that the simplest and best way to assure, at least for some period of time, that all will follow the same guidelines is for the Congress to pass legislation.

If these assumptions are correct, then the committee concludes that the bill H.R. 11192 establishes a reasonable basis for temporary regulation of all recombinant DNA research. It must be kept in mind, however, Secretary of Health, Education, and Welfare Joseph A. Califano, Jr., stated in releasing an Interim Report of the Interagency Committee on Recombinant DNA Research on March 16, 1977, that: "legislation in this area would represent an unusual regulation of activities affecting basic science."

For these reasons the committee intends that this legislation be viewed as an "experiment." It is important that the experiment be conducted wisely, and that it be considered a learning experience. The two-year regulation period should be an empirical one to determine which of the legislative and regulatory provisions work well and which don't—and, importantly, if a need for continuation of the legislation exists. This view is implicit in several of the committee's amendments to the bill.

SECTION-BY-SECTION SUMMARY OF H.R. 11192

Title I—Interim Regulation of Recombinant DNA Activities

Definitions (section 101)

Section 101 of the bill defines the term "recombinant DNA" explicitly and operationally as it is done in current NIH Guidelines. "Recombinant DNA activity" is defined as the possession in a State of recombinant DNA and any activtiy (including research and transportation) undertaken for the production of recombinant DNA.

Extension of the recombinant DNA guidelines (section 102)

Section 102(a) of the bill provides for the extension of the requirements of sections II (Containment) and III (Experimental Guidelines) of the NIH Guidelines to all recombinant DNA activities beginning on the tenth day after the date of enactment and ending twenty-four months after such day. Before the expiration of the ten-day period the Secretary of HEW is required to publicize and make available the requirements of sections II and III of the Guidelines. The Secretary is authorized to amend the requirements, in accordance with the Administrative Procedure Act, if he determines that such an amended requirement would be sufficient for the protection of health and the environment.

Section 102(b) authorizes the Secretary to exempt from the requirements any recombinant DNA activity which he finds does not present a significant risk to health or the environment.

Section 102(c) requires each individual or entity which is responsible for the conduct of any recombinant DNA activity or which will be responsible for such an activity to be commenced during the period the guidelines are in effect to report to the Secretary such individual's or entity's name, a description of such activity, an identification of the place or places in which such activity is or will be conducted, and assurances satisfactory to the Secretary that such activity will be carried out in accordance with the requirements of the guidelines.

Section 102(d) requires the Secretary within 90 days of the date of enactment to issue regulations for the administration of the requirements of the proposed legislation.

Prohibited acts and penalties (section 103)

Section 103(a) prohibits any person from conducting any recombinant DNA activity in violation of any requirement of section 102 of the bill; moving recombinant DNA in violation of an order issued under section 105(c) (administrative detention); or failing or refusing to establish or maintain records, make reports or provide information, or permit entry to instruction as required by the proposed legislation.

Section 103(b) provides that any person who violates section 103(a) would be liable for a civil penalty of up to $5,000 for each violation. Each day such a violation continues would constitute a separate violation.

Section 103(c) authorizes the Secretary, in instances in which a person has violated section 103(a) in carrying out a project funded by a grant from HEW, to cancel such grant or withhold payments under such grant until he determines such person will carry out such project in accordance with the requirements of the guidelines.

Injunction authority—emergency procedure (section 104)

Section 104(a) confers upon U.S. district courts the jurisdiction over civil actions to restrain violations of section 103(a). Such actions are to be brought in the judicial district where the violation occurred or where the defendant transacts business. In such actions, process may be served on defendants and subpoenas served in any judicial district.

Section 104(b) confers upon U.S. district courts jurisdiction over civil actions for (1) the seizure or destruction of recombinant DNA, or material used in recombinant DNA activity, which was involved in a violation of section 103(a) or which presents or may present a significant risk to health or the environment or (2) any other appropriate relief to prevent the production or movement of such recombinant DNA or material. Such actions are to be brought in the judicial district in which the recombinant DNA or material is found.

Inspections (section 105)

Section 105(a) authorizes individuals designated as inspectors by the Secretary for purposes of enforcement of the requirements of section 102 to enter and inspect any place in which a recombinant DNA activity is being conducted or in which the inspector has reasonable grounds to believe such an activity is being conducted. Such an inspection is to be conducted during normal business hours (if any) of the place, and may extend to all things in the place bearing on whether the activity is being conducted in accordance with the applicable requirements. Before entering a place, an inspector is to present appropriate credentials and a written notice to the person in charge and clearly inform such person of his authority. Upon competition of any inspection, the inspector is to provide the person in charge with a preliminary report summarizing any condition or practice which indicates a violation of the applicable requirements. Within 30 days the inspector is to prepare a final written report.

Section 105(b) requires a person in charge of a place inspected, upon request of the inspector, to provide samples of recombinant DNA or materials used in or produced by any recombinant DNA activity conducted in such place to enable the inspector to determine if the applicable requirements are being met.

Section 105(c) authorizes an inspector to order recombinant DNA or materials used in or produced by any recombinant DNA activity detained for a period not to exceed 20 days if he has reason to believe it is involved in a prohibited act under section 103(a) or presents a significant risk to health or the environment. If the Secretary determines a longer period is necessary in order to institute a civil action under section 104(b), he may authorize a detention period of up to 30 days.

Section 105(d) provides that no inspector shall be required to obtain a search or inspection warrant before inspecting a place.

Section 105(e) provides that an individual who is engaged in or has a direct financial interest in a project involving a recombinant DNA activity cannot be designated as an inspector of such project.

Effect on State or local requirements (section 106)

Section 106(a) provides that (except as authorized under section 106(b)) no State or political subdivision thereof may establish or

continue in effect any requirement for the regulation of recombinant DNA activities.

Section 106(b) establishes conditions and procedures under which States and political subdivisions thereof may prescribe requirements with respect to recombinant DNA activities. It requires the Secretary, upon application, after notice and opportunity for an oral hearing, and after considering local conditions, to issue an order exempting a State or local requirement from subsection (a) if (1) the requirement is the same as, or more stringent than, a requirement under section 102(a) and (2) the requirement is necessary to protect health or the environment. The oral hearing is to be commenced not later than 60 days from the date the application is submitted. The presiding officer at the hearing is to make a written recommendation to the Secretary respecting approval of the application. Within 60 days of the conclusion of the hearings or 120 days after submission of the application, whichever occurs first, the Secretary must approve or deny the application. The Secretary's decision must be in writing and, if a hearing was conducted, the decision must contain the recommendation made by the presiding officer, and must include a complete statement of the reasons for the Secretary's decision.

Training and studies (section 107)

Section 107(a) authorizes the Secretary to conduct and support training in the safe handling of recombinant DNA.

Section 107(b) requires the Secretary to conduct or support on a continuing basis studies assessing the risks to health and the environment of recombinant DNA activities. In addition, it authorizes the Secretary, by order, to make the requirements of section 102 inapplicable to such risk assessment studies. Such orders are to be published in the Federal Register together with a statement of the basis for the order.

Relationship to other Federal laws (section 108)

Section 108(a) specifies that title I shall not affect the authority of any Executive Agency to regulate recombinant DNA activities under any other Act.

Section 108(b) establishes that the Secretary shall not be deemed to be exercising statutory authority under section 4(b)(1) of the Occupational Safety and Health Act of 1970, in exercising any authority under title I of this act.

Section 108(c) assures the "sunset" provisions of Title I.

Title II—Commission for the Study of Research and Technology Involving Genetic Manipulation

Section 201 provides for the establishment of a thirteen member Commission for the Study of Research and Technology Involving Genetic Manipulation. The members of the Commission are to be appointed by the President from individuals distinguished in such fields as medicine, law, ethics, the biological, physical, and environmental sciences, philosophy, humanities, health administration, government and public affairs.

Section 202 sets forth the duties of the Commission which include (1) the conduct of a study of Federal policy regarding activities involving the genetic modifications of organisms and viruses, and (2) a

study of the long-term consequences of the development of a technology capable of accomplishing the genetic modification of organisms and viruses.

Section 203 requires the Commission, in carrying out its duties, to hold public hearings as appropriate, and requires the head of any U.S. department or agency to furnish to the Commission, upon its request, information necessary to enable the Commission to carry out its duties.

Section 204 requires the Commission, within 18 months after the date of enactment, to report to the Congress the preliminary results of the Commission's study with respect to Federal policy regarding activities involving the genetic modification of organisms and viruses. It further provides that the Commission, within 30 months after the date of enactment, is to complete its studies and make recommendations to the Congress, the President, and appropriate Federal agencies regarding action the Commission determines should be taken to promote, regulate, or review activities involving the genetic modification of organisms and viruses. Finally, it provides that the Commission shall terminate within 60 days of the date upon which is completed its studies and made its recommendations.

COMMITTEE AMENDMENTS

All of the amendments made by the Committee on Science and Technology to the Findings and to Title I of the bill were made to emphasize or clarify intentions already suggested or specified by the Committee on Interstate and Foreign Commerce in Part 1 of this report.

Some of the amendments to Title II are substantive.

Findings

Section 2(3). (P. 2, Line 17.) Substitute "may be" for "is."

The amendment is designed to prevent misinterpretation of the fact that recombinant DNA research, at present, carries with it no known or demonstrated risk—only that such a risk may be uncovered in the future.

Title I

Section 102(d). (P. 7, Line 7.) Substitute "shall" for "may."

The amendment makes it a requirement that NIH guidelines on DNA research will contain appropriate provisions for reporting and for local assistance in the enforcement of the Act.

Section 102(d). (P. 7, Lines 10–14.) Add the following:

> , as well as provisions giving due consideration to the need for protection against improper or unwarranted disclosure of privileged, confidential, or proprietary information, trade secrets, and information held under patent rights.

The amendment puts into the statute, as well as the report, a requirement that NIH guidelines give due consideration to the special problems of industry and non-profit groups engaged in DNA research with particular regard to proprietary information.

Section 103(b)(2). (P. 8, Line 22.) Substitute "may" for "shall."

The amendment is intended to insure that the Secretary of HEW, in his enforcement procedures, not be required to levy civil penalties in every case of violation of the guidelines, no matter how trivial, tech-

nical or unintended. Since the language involved, however, can be read several different ways, the change made by this Committee has created a different problem concerning enforcement methodology. It is expected that a corrective amendment will be offered on the floor.

Section 108. (P. 17, Line 1.) Add new subsection:

> (c) No part of this title shall remain in effect beyond the end of the period specified in section 102(a)(1).

The addition assures that all parts of Title I expire at the end of 2 years. Without this provision certain sections of Title I would apparently remain in force indefinitely.

Title II

Section 201(a) and (b). (P. 17, lines 6–7, 12–13.) Substitute "the President" for "Secretary" as the authority to appoint members of the genetic manipulation study Commission.

The amendment was prompted in order to assure a broader input of recommendations for Commission membership. Since considerable genetic research is done or supported by agencies of government other than NIH, it appeared reasonable that their representatives have a voice, through the President, in making recommendations. The Commission itself, however, is retained under the Secretary of HEW.

Section 201(b). (P. 17, line 15.) Substitute "in such fields as" for "in the fields of."

As first reported, the bill would limit membership on the Commission to certain fields or scientific disciplines. The amendment makes the fields specified in the bill exemplary but not exclusive.

Section 202(1)(C). (P. 19, lines 16–17.) Substitute "such risks to health and the environment as may be presented" for "the risk to health and the environment presented."

The amendment is to avoid inducing conclusions that these risks have been shown to be conclusive as of this time, whereas the risks, if any, are currently unknown.

Section 202(2)(B). (P. 10, line 6.) Add the word "environmental."

The additions assures inclusions of environmental factors in the Commission's studies.

Section 202(2)(B). (P. 20, lines 8–10.) Add the phrase: "as well as the significance of lessons learned through recombinant DNA research and its allied science policy issues. . . ."

The addition directs the Commission to evaluate experiences gained through issues associated with DNA research as it considers the implications of future genetic technology.

Section 202. (P. 20, lines 11–14.) Add new subsection:

> (C) a comprehensive assessment of the status and application, achieved or anticipated, or genetic manipulation technology in other nations engaged in such activities.

The amendment adds a new dimension to the "long-term consequences" portion of the Commission's activities. It emphasizes the need to conduct Commission surveys in an international context.

Section 204(a). (P. 20, line 25.) Substitute "Commission" for "Secretary."

The amendment is for purposes of conformance only.

COMMITTEE VIEWS

General

In Part 1 of this report, the Committee on Interstate and Foreign Commerce presents a full sectional analysis and discussion of its views. The Committee on Science and Technology submits herewith its views on the bill as a whole, and provides additional views on selected sections.

"Legislation in this area would represent an unusual regulation of activities affecting basic science." This statement by Secretary Califano enunciates the basis for the Committee's concerns regarding H.R. 11192. It would be unfortunate if this period in our Nation's history were someday to be named the Science Regulation Era, but at times that possibility does not seem unlikely. It is disturbing to see another segment of human endeavor laid open to regulation, particularly at a time when people are upset by the mushrooming Federal bureaucracy and the accelerating growth of encumbering and restrictive controls in all aspects of their lives.

The regulation of recombinant DNA research may be an opening wedge into future regulations of other areas of basic research. This fact is viewed by many people—especially by scientists—as a major attack on the freedom of scientific inquiry.

Scientific inquiry, of course, is not an absolute freedom, nor is science automatically exempt from all restraints or regulation. There has been no question of the propriety of regulating research involving human subjects or radioactive materials. When the freedom of scientific inquiry is in conflict with other freedoms which are valued at least as much, then it is certainly proper to constrain scientific inquiry. The difficult questions are: what constitutes a truly serious conflict, and what type of social control is appropriate? Matters such as these are what this Committee and the Committee on Interstate and Foreign Commerce both attempt to address under "Need for Legislation."

The Committee on Science and Technology suggests that the real threat to the freedom of scientific inquiry may be less likely to come from those who would restrict or regulate research to protect the public health, safety or other values we cherish than from those who believe there are some things man just should not seek to know. Thomas Jefferson once stated that "There is no truth on earth that I fear to be known." This sentiment seems as applicable now, after several centuries of unparalled scientific advance, as it was then. Equally crucial is the very thorny question: should government become the arbiter of knowledge? Were such events to crystallize then freedom would truly be gone.

The bill H.R. 11192 was developed only to protect the public health and the environment. As stated by the Committee on Interstate and Foreign Commerce, "legislation is justified only to the extent that safety guidelines are necessary."

Just as recombinant DNA research might present a risk to health and the environment, the precedent set by this legislation may present a risk to the freedom of scientific inquiry. The committee is concerned that any instance of regulating research might facilitate the adoption of another. As in any area of regulation, the government must guard

against excessive zeal to protect society from all risks, however minor. Such activity would particularly cripple science—the principal tool that our civilization has fashioned to improve the condition of man in this world.

Specific Sections

Section 2. Findings

The committee amendment which substitutes the words "may be" for the word "is" (page 2, line 17) is designed to prevent misinterpretation of the fact that recombinant DNA research, at present, carries with it no known or demonstrated risk—only that such a risk may be uncovered in the future. It should be clear that the committee is not presuming that recombinant DNA research does in fact pose a risk to health or the environment.

Section 101. Definitions

(2) Recombinant DNA

Although the report of the Committee on Interstate and foreign Commerce states that subparagraph (A) contains an operational definition of recombinant DNA, designed to be consistent with that in the proposed revisions to the NIH Guidelines, the definition in the legislation is not precisely the same as the existing guidelines nor is it precisely the same as the proposed revisions to the guidelines. The bill defines the term recombinant DNA as:

> (A) molecules which are formed by joining together DNA segments outside of living cells and which have the capacity to enter a cell and to replicate in such cell either autonomously or after they have become an integrated part of such cell's genome; or
>
> (B) are the result of a replication of the DNA molecules described in subparagraph (A).

The NIH guidelines now in effect (June 23, 1976) define recombinant molecules as:

> molecules that consist of different segments of DNA which have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host's genome.

The proposed revisions to the NIH guidelines published in the Federal Register, vol. 42, no. 187, September 27, 1977 define recombinant DNA as:

> molecules consisting of segments of DNA from different genomes which have been joined end-to-end outside living cells and have the capacity to infect some host cell and be maintained therein. These Guidelines, however, pertain only to "novel recombinant DNAs", here defined as molecules that consist of segments of any DNA from different species that are not known to exchange chromosomal DNA by natural physiological processes.

It is important not to confront the investigator in recombinant DNA research with an ambiguous situation with regard to the research which will be affected by the proposed legislation. Even though

section 102(b) provides the Secretary with flexibility for exemption of certain recombinant DNA activity which the Secretary finds does not present a significant risk to health or the environment, it is desirable to have as complete agreement as possible between the definition of the activity to be regulated by the legislation and the definition eventually implemented by the Secretary as revisions of the Guidelines.

Since informal discussions with representatives of the National Institutes of Health indicate that the definition changes may not be implemented as presently proposed, it is important for the Congress to attend to such changes prior to enactment of the legislation. The definitions within the legislation and the definitions of the Guidelines in effect at the time of enactment of the legislation should be consistent. If the revisions to the Guidelines are approved before the legislation is enacted, then the definition within the legislation should be examined for conformance with the definition within the Guidelines. If the legislation is enacted first, then the legislative history should show that it is the intention of the committee that the definition of recombinant DNA should be consistent with the definition presented in the Guidelines; where there are minor differences, the definition within the NIH Guidelines should apply.

Section 102. Extension of the Recombinant DNA Guidelines

H.R. 11192 provides the Secretary of Health, Education and Welfare with a great deal of flexibility in implementing the interim regulations. The committee concurs in the need for this degree of flexibility in the legislation, especially as it relates to the revision of the NIH Guidelines and to the exemption of those experiments which do not present significant risks to health or the environment. It is important that the Guidelines continue to be revised regularly, relaxed or strengthened in the light of accumulated experience; furthermore, if and when conditions warrant, they should be abandoned.

Concern has been expressed that the broad exemption power granted to the Secretary may encourage numerous individual requests for exemptions. The committee hopes that this situation does not occur; it would seem poor administrative practice for the Secretary to be routinely involved with such decisions on a project-by-project basis.

The committee amendment which changes the word "may" to "shall" (page 7, line 7) would require the Secretary to include in the proposed regulations provisions for reporting and for local assistance in the administration and enforcement of the regulations. The committee expects that the "local entities" referred to in the legislation will usually be local biosafety or biohazard committees. The amendment would ensure input from these valuable groups.

The committee notes with approval that, as part of the revision of the NIH Guidelines, the NIH is considering substituting the term "biosafety committee" for the term "biohazard committee" throughout the Guidelines. In support of this trend towards more positive thinking, IBC's or LBC's will be referred to as "Institutional" or "Local Biosafety Committees" in the discussion which follows.

The committee concurs with the Committee on Interstate and Foreign Commerce that the regulations promulgated by the Secretary should include guidelines respecting membership on biosafety com-

mittees. It is important that some of the members be drawn from the public at large. Laboratory workers, both non-professional as well as professional, should be considered for membership. Public members of industrial Boards of Directors may be good candidates for certain biosafety committees.

It is expected that such guidelines would be sufficiently flexible to provide for experimentation across the country. Depending on relationships within a community, traditions of the area, and so forth, the composition and nature of biosafety committees might well be quite different, as might the degree of involvement such committees would have in administering and enforcing regulations. The knowledge accumulated over the next two years from these experiments should be valuable in discussions of the broader issues of public participation.

It is impossible (not to mention objectionable) for the Federal government alone to assure compliance with the regulations. Therefore it seems essential that responsibility for primary oversight of recombinant DNA research lie with the biosafety committees. Their importance should be emphasized.

Proprietary Information

The committee also amended H.R. 11192 to require the Secretary to include in the regulations "provisions giving due consideration to the need for protection against improper or unwarranted disclosure of privileged, confidential, or proprietary information, trade secrets, and information held under patent rights." This amendment gives the Secretary no new authority, but it does make explicit the desire of both the Commerce and Science Committees that the regulations contain adequate safeguards for nonprofit, industrial and commercial entities equally with regard to protection of their data and information of a proprietary nature.

All private and public witnesses who testified on H.R. 11192 before the subcommittee expressed some concern about these problems. It was also noted that the Department of Commerce is less than fully satisfied that this bill will meet the needs of the protection of trade secrets, proprietary rights, and intellectual property.

The question of how proprietary information in this area is going to be handled by the government is important because proposals to do recombinant DNA research are to be submitted before the research is done. Recombinant DNA research in universities as well as industrial research laboratories will involve potentially patentable information, and suitable protection should apply whether the information is submitted by a private company, a university, or any other individual or institution.

The regulatory provisions of H.R. 11192 require that the Government obtain a great deal of information about certain basic research projects which it normally would have no reason to obtain. Once again the committee is concerned about precedents which may be set if adequate consideration is not given to this issue. In the particular case of recombinant DNA research, problems may not be as serious as they might be since it can already be shown that the information may have commercial or proprietary value. If regulations are ever imposed upon other areas of basic research which cannot make that showing, there could be serious problems in the future.

Premature disclosure of such information is of great concern to both the nonprofit as well as commercial interests. Although there is no question that the interest of public health and safety are paramount, the "risk/benefit equation" will not be meaningfully balanced in the public interest if adequate protection of confidential is not provided. As discussed above, such information may have real or potential patent value both for nonprofit as well as commercial entities and untimely release could make it virtually impossible to obtain patents in the United States or in foreign countries. In other cases the research protocols or results are the most important asset of the laboratory scientist—the "intellectual capital" upon which future grant or contract applications, or publications affecting his career, depend.

Under the provisions of H.R. 11192, premature disclosure could occur in a number of ways, depending on the nature of the regulations eventually promulgated by the Secretary. For example, it conceivably might occur in registration of research protocols, through inspections, through availability of information to members of biosafety committees, through the activities of the Commission, and the like. It is important to note that in all such instances the applicability of 18 U.S.C. 1905 is clear. This Federal statute prohibits the release by any employee of the Federal government of "trade secrets, processes, operations or apparatus" obtained pursuant to this bill. It is only because of the existence of this provision that it is unnecessary to write any additional provision into the legislation. In fact, if it were not for the protection afforded by 18 U.S.C. 1905 there would clearly have been a need to put an additional provision into the legislation.

Following publication of proposed regulations in the Federal Register, "the Secretary shall give interested persons an opportunity to submit written data, views, or arguments on such regulations and may provide opportunity for the oral presentation of views and arguments." Because of the special concerns and interests of industry, the term "persons" should clearly include commercial entities conducting recombinant DNA research.

Environmental Impact

The Committee on Interstate and Foreign Commerce deleted a provision within section 102 which would have made the provisions of the National Environmental Policy Act (NEPA) of 1969 inapplicable to any action taken by the Secretary under title I of the bill. The Committee on Science and Technology agrees with the logic of this decision and supports the action taken by the Commerce Committee as further discussed in its report.

As pointed out during testimony by the Director of NIH before the subcommittee on April 11, 1978, to fulfill the NEPA requirement DHEW will conduct an assessment of the environmental impact of the standards and regulations (i.e., of the NIH Recombinant DNA Guidelines). The NIH will then, based on the assessment document, make a determination as to whether an Environmental Impact Statement (EIS) is required for a specific change in the standards and regulations being proposed.

NIH did file an environmental impact statement on the recombinant DNA Guidelines in October 1977 and is conducting an assessment of the environmental impact, if any, of the proposed revisions to the

existing Guidelines. It is the committee's view that this procedure being followed by the NIH is the most appropriate to produce decision documents and put changes into effect as rapidly as possible and in accordance with the Administrative Procedures Act. The provisions of H.R. 11192 should not imply that any change in the guidelines automatically requires the completion of the longer procedures required for processing an EIS on all actions. The Secretary should have freedom to move expeditiously to make changes in the guidelines as necessary to protect the environment and health, but he should be equally free to insure an optimal environment for research. The assessment procedure to determine the need for an EIS should provide maximum flexibility during the experimental period of this legislation.

Conflict of Interest

In a dissenting view to the report of the Committee on Interstate and Foreign Commerce, several Members expressed a concern that "H.R. 11192 places NIH, through the Secretary, in the position of being both promoter and regulator, a situation similar to that of the now-defunct Atomic Energy Commission. There is an obvious conflict of interest inherent in this situation." Based on the Administration's plan for implementation of the regulatory provisions of this bill, as outlined in testimony before the subcommittee, it is doubtful if such an inerent "conflict of interest" exists. Regarding earlier legislative proposals the Administration stated that:

> NIH [will] recommend the revisions in the guidelines, review and clarify the technical issues, and handle, if you will, the standard setting, the philosophy, the scientific input, and then turn over to [the Center for Disease Control] the functions of licensing facilities and maintaining the registry and operating and promulgating standards. Both organizations would obviously have to be involved in training workers and in working with those outside the Federal Establishment as well as inside that are involved in recombinant DNA research.

The record also shows that:

> NIH, for the past 18 months, has worked closely with the . . . (CDC) concerning safety aspects of the Guidelines. . . Close coordination and consultation with the Food and Drug Administration and the Environmental Protection Agency will be essential since these agencies' regulatory authorities will come into play when recombinant DNA research inventions are ready for commercial development. The Occupational Safety and Health Administration will exercise its regulatory authority in the workplace.

The committee's interest in resolving potential conflict of interest situations within NIH stems not only from usual concerns, but also from a concern that turning NIH into regulatory agency would do great damage to its principal function—the support of high quality research. The committee is satisfied that efforts are being made to meet these concerns.

Section 103. Prohibited Acts and Penalties

The committee agrees with the Committee on Interstate and Foreign Commerce that it is important for agencies other than DHEW which support recombinant DNA activities to cooperate with the Secretary should he request cancellation or withholding of grant payments for violation of regulations. The committee would also like to emphasize its agreement that any penalties or sanctions be administered carefully and with fairness to all concerned.

To insure that the Secretary, in his enforcement procedures, not be required to levy civil penalties in every case of violation of the regulations, no matter how trivial, technical or unintended, the Committee substituted the word "may" for "shall" (page 8, line 22). Since the language of this section, however, can be read several different ways, the change made by the Committee has created a different problem concerning enforcement methodology. It is expected that a corrective amendment will be offered on the floor.

Section 104. Injunction Authority; Emergency Procedure

In its report the Committee on Interstate and Foreign Commerce states that it "views this provision as one which citizens can use to ensure enforcement of the guidelines." In other words it is intended that any citizen can bring action in Federal court to obtain an injunction for an alleged violation of the guidelines.

The language of this section itself, however, does not specify that private citizens have a right to bring individual enforcement suits. For this reason, a private right of action under section 104 will exist only if it is implied from a reading of the statute, its intent, and underlying purposes. Implication of a private remedy is not a practice the courts undertake lightly. In fact, the Supreme Court has articulated a four-part test to determine the existence of private causes of action in statutes that do not provide them.

For this reason it appears desirable to include explicit statutory language for private enforcement of the guidelines. The usual statutory way of dealing with legal concerns of a citizen is to provide that such persons give notice to the Attorney General, who will then make a study and decide what legal action may be required; and to the facility involved, which can similarly determine whether voluntary action is warranted. If neither takes action, a civil suit would be permitted. This kind of provision for "citizen civil action" is found in other regulatory statutes and may be worth consideration here. Since amendment of this section in the Committee on Science and Technology was considered out of order, such amendment might be offered on the floor of the House.

Section 105. Inspections

As noted in the report of the Committee on Interstate and Foreign Commerce, it is possible to specify:

> four considerations utilized by the Supreme Court in determining whether an administrative inspection authorized by Federal statute is constitutional:
>
> (1) was preceded by adequate notice to the person in charge as to the identity of the persons conducting the inspection and the legal basis for the action?

(2) was the inspection carefully limited in time, place and scope?

was the inspection of central importance to a valid Federal purpose?

(4) is there a long history of regulation of the inspected industry?"

The Interstate and Foreign Commerce Committee notes that, "obviously, the fourth consideration—history of extensive Federal or State regulation—is a test that cannot be met." Additional concern has been expressed by some that the authorization of warrantless administrative searches by this bill is not in accord with Fourth Amendment protections against unreasonable searches or a number of pertinent Supreme Court decisions.

The committee is not prepared to give an opinion on these matters; however, considering the seriousness of the issue it is suggested that this particular aspect of the legislation receive further attention by the relevant Committees of Congress and by the Commission established in Title II.

Section 106. Effect on State and Local Requirements

One of the most discussed and debated subjects by both House committees which considered the bill, is the so-called "preemption" clause, Section 106 of the bill.

In essence, this section states that Federal regulations of recombinant DNA research shall take precedence over any State or local regulations on the subject unless (1) the local regulations are more stringent than the Federal ones and (2) it can be shown that the stronger restriction is "necessary to protect health or the environment."

The Committee on Science and Technology made no change in this section, the chair having ruled its amendment not germane to the committee's authority under sequential referral rules.

But the committee did consider the various implications of the section, and it was clear that strong views exist with regard to preemption along several different lines.

Clearly there are those on the committee who consider this section one of the most important in the bill. They feel that without it, a host of varying local controls would spring up which would make useful recombinant DNA research almost impossible. They oppose any suggestions for change which might "water down" the section.

Some members of the committee might prefer to see the section eliminated on grounds that preemption is but another instance of the Federal Government interfering in the rights of States and localities to make rules which they conceive as necessary for their own safety and protection.

And, also clearly, there are those who would prefer to take a somewhat in-between, or compromise, position. For the most part those who espouse this procedure have concentrated on the proposal that the word "necessary" in Sec. 106(b)(2) be eliminated in favor of "reasonable." This, they argue, would provide a more flexible formula for permitting local regulations to prevail—based upon "reasonable" requirements for local control rather than "necessary" ones. They believe the change would further allow a greater voice in the situation for States and localities regardless of which set of regulations governs.

With reference to the foregoing semantic discussion, the testimony of Administration witness, Dr. Donald Fredrickson, Director of NIH, is pertinent. Dr. Fredrickson supported the bill as it stands and emphasized that "we strongly favor preemption." He then added:

> It is the Administrations' view that a standard of reasonableness, as determined by the Secretary, rather than necessity as in H.R. 11192, should apply when state or local governments petition to have their requirements govern. I would like to point out that the NIH Guidelines provide for strict standards to govern this research, and in no sense can they be considered minimum national standards. Thus, I believe that state and local governments will recognize the prudence and conservatism of these standards and find them to be a high standard for the protection of health and the local environment.

The overall impression left with the committee is thus one of some ambivalence. However, it is not a matter on which the committee, as a committee, need have a position. And indeed it does not.

What viewpoint might have emerged as a committee position, if a decision on Section 106 had been called for, is very difficult to assess. The differences described in the foregoing resulted from a lively but truncated debate—and did not include expressions of opinion from a majority of the members. There seems little doubt, however, that a very broad range of opinion will be heard when the bill reaches the floor.

Section 107. Training and Studies

It is important for data to be gathered on the risks, if any, of this research and the scientific community is to be commended for its actions four years ago pointing out the possibility of risks which might have accompanied some of the experiments they were planning. Their actions have been rightly labeled by scientists and others as a landmark in the history of the social responsibility of scientists.

Accumulating scientific evidence and increasing experience in the laboratory has apparently diminished the concern among most scientists regarding the magnitude of risk associated with this research. Many biochemists now believe that organisms containing recombinant DNA could not be as dangerous as many known disease-producing organisms which are cultured in thousands of medical laboratories every day.

As the Subcommittee on Science, Research and Technology has noted in its report, the recombinant DNA controversy has brought into question the ability of society to handle new information. In this area of risk assessment, it has also brought into question the ability of society to deal with a lack of information—in other words, the ability of society as a whole to deal with what is as yet "unknown."

Much of discovery in science is unexpected—so much so that "basic research" has become associated with a certain willingness to explore the "unknown." Thus it may be that scientists generally are more comfortable operating in these realms—where there is a lack of information—than the average person.

H.R. 11192 states that "while no hazard has been demonstrated" there is nonetheless a need for legislation. Despite this conclusion it

remains much more difficult to fashion legislation to protect society against its fears than it is to protect it against known dangers. With DNA research, the very existence, much less the magnitude and nature, of the risks presented are yet a matter of speculation.

While scientists may be at ease with the knowledge that the statistical probability of some event occurring is "ten-to-the-minus-whatever," many people are not—and what is needed is an orderly demonstration of just what those risks are. All participants in the debate over recombinant DNA research need better information about actual risks in real experiments. Public anxiety, initially generated by the scientists, cannot be reversed until this information is available and subjected to adequate peer review.

Developing scientific information on the risks or lack thereof in recombinant DNA research requires flexibility in regulation. H.R. 11192 provides the flexibility. The specific authority granted in this section to issue exemptions for high-risk assessment experiments in high-containment conditions is an essential feature of the bill.

Section 108. Relationship to Other Federal Laws

The committee amended this section to add a new subsection (c) that assures that all parts of Title I expire at the end of the two-year period encompassed by the legislation. Without this provision certain sections of Title I would apparently remain in force indefinitely.

Section 201. Establishment of a Study Commission

The committee amended this section to make the President, instead of the Secretary, the authority to appoint members of the genetic manipulation study Commission. The amendment was prompted in order to assure a broader input of recommendations for Commission membership. Since considerable genetic research is done or supported by agencies of government other than NIH, it appeared reasonable that their representatives have a voice, through the President, in making recommendations. The Commission itself, however, is retained under the Secretary of HEW.

One of the criticisms of the early reactions of potential risk in recombinant DNA research was that those with broad experience in the transmission of contagious disease were not brought in to examine the potential hazards of work with an organism such as *Escherichia coli*, the primary host in most recombinant DNA work. If such individuals had participated in the early evaluations, perceptions of risk might have been quite different. There is every reason to believe that an alternative microorganism or several microorganisms eventually might be certified for work in recombinant DNA research. If the Commission is to function effectively in its evaluative tasks, persons should be appointed to it who have a working knowledge of the field of genetic manipulation. In this regard the Science and Technology Committee supports the views as expressed in the Commerce Committee report on this legislation.

The committee thus believes that the provisions for appointment of individuals to the Commission should be broad enough to include opportunities to appoint individuals who are expert in the fields of epidemiology, molecular biology, and microbiology as well as the other fields suggested in H.R. 11192 as reported by the Commerce Commit-

tee. The amendment to strike "the fields of" and insert in lieu thereof "such fields as" is intended to broaden the scope of the appointments.

In other sections of the bill which follow, the committee has increased the mandate of the study Commission. Although the provisions in this section are quite flexible regarding the appointment of staff personnel for the Commission, the committee expects that staffing for the Commission will not be excessive. (See estimate of Congressional Budget Office.)

Section 202. Duties of the Commission

This section assigns responsibilities to the Commission for the study and evaluation of recombinant DNA activities and also to other "activities involving the genetic modification of organisms" and "genetic manipulation technologies".

It should be recognized that these are very broad terms which could conceivably be construed to mean that the Commission should evaluate the impact of all research or technological activities involving some direct genetic modification of organisms. The term "genetic manipulation" includes research such as recombinant DNA; laboratory induced cell fusion for the purpose of producing a recombination of genetic material either for study of recombination processes or production of viable cell cultures or organisms; *in vitro* fertilization involving human or animal cells; cloning of animals by asexual nuclear transfer; direct synthesis of genes; reverse *in vitro* synthesis of genes (intermediate synthetic techniques using messenger RNA, etc.); gene therapy; and other similar techniques for reproducing or affecting the hereditary traits of an organism. Because such techniques may induce changes similar to those induced by recombinant DNA techniques, the Commission should consider them along with recombinant DNA in order to provide the Congress with recommendations on the need for additional legislation.

However, such broad terminology as "genetic modification" or "genetic manipulation" might also be construed to mean that the Commission should take cognizance of all manner of genetic techniques. These would include such established techniques as selective hybridization, common in the selective breeding of plants and animals; classic genetic methodologies in microbiology and virology; vegetative cloning; or such methods of animal propagation as artificial insemination.

The committee does not believe that the Commission should be charged at this time to undertake a total assessment of the ethical, moral, social or other implications for the entire field of genetics. The ground to be covered seems too broad and complex for that. The committee suggests, therefore, that the Commission established by H.R. 11192 should devote its primary attention to the potential impact of recombinant DNA and closely associated types of genetic manipulative techniques. The short time for study involved and the rather limited resources of the Commission must be focused in this way if the analysis needed by the Congress to determine the need for extension, modification or elimination of this experimental, two-year legislation is to be useful.

As reported by the Committee on Interstate and Foreign Commerce, the Commission for the Study of Research and Technology Involving Genetic Manipulation serves two purposes in H.R. 11192. First, it will evaluate the operation of the interim controls as well as

other provisions of Title I. The evaluation will determine whether the controls should extend beyond the initial period. Second, the Commission must undertake a sort of "technology assessment" of long range applications of recombinant DNA research discoveries and techniques.

With respect to the first of these two studies, the committee amended the phrase "the risk to health and the environment presented" to read "such risks to health and the environment as may be presented" to indicate that it is not presumed that such risks have been shown to be conclusive as of this time. In fact the risks, if any, are currently unknown.

Science Policy Issues

Regarding the second study, the Committee made several amendments to the bill. The controversy over recombinant DNA research has provided a unique opportunity to explore the interaction between the pursuit of basic research and public concerns over health, safety and the social and environmental effects of applying recombinant DNA techniques. The committee believes that the lessons of this experience could be of great benefit in the future development of science policy at both the local and Federal level.

The expansion of the scope of the Commission's duties to consider "the significance of lessons learned through recombinant DNA research and its allied science policy issues" is thus an important addition. In its extensive hearings on the "Science Policy Implications of DNA Recombinant Molecule Research", the Subcommittee on Science, Research, and Technology, noted as a major finding that all parties, government and non-government, need to maintain an awareness of the evolution of new methods, models, and institutions for resolving public policy questions.

In this context, many issues are confronted, including the constitutional basis of regulation of basic or applied research; balancing the need to insure safe conduct of research against implied first amendment rights of free inquiry; the need to anticipate social, ethical, economic and environmental consequences of research or its application; methods for improving communication between the scientific community and the general public; techniques, short of direct regulation, for alerting society to potentially hazardous areas of basic and applied research; determination of various points on the "pure-applied research continuum" at which different degrees of public involvement may be appropriate; investigation of the ability of the public to assimilate scientific concepts when required to develop public policy; the legitimacy of, as well as techniques for, public involvement in the stimulation and regulation of basic and applied research; the improvement of risk and benefit assessments; determination of the appropriate level of governmental and public involvement in research regulation when necessary; the relative efficiencies of peer review and public review of the risks and benefits of research; techniques for responding to warnings by scientists concerning possible dangers arising from research; and the improvement of predictive assessments to determine if untried technological alternatives should be pursued.

As previously noted, the Commission does not have the time or the resources to examine every issue. Those salient to the interaction of

public understanding and policymaking and to the conduct of research should be the focus of the Commission's efforts. Traditional forms of assessment do not seem to work well in areas of high uncertainty about risk. One value of this Commission is in serving as a forum for public inputs into such difficult assessments. If there are actions which the Congress can take to encourage greater or different forms of participation by representative public and scientific groups, or legislative initiatives which should be taken, then these, as identified by the Commission in its studies, should be made known in the final report of the Commission.

International Phase

Finally, the committee added a subsection (202(2)(C)) directing the Commission to follow and report on the research and achievements of genetic manipulation technology in other countries.

Testimony during the subcommittee hearings of this Congress has shown frequently that recombinant DNA research is an activity being carried on in a number of scientifically advanced nations. The testimony also suggests strongly that regulating DNA research in the U.S., if too restrictive, will only result in a pronounced—and possibly damaging—technological lag. That lag may be difficult to overcome in a number of ways if it develops, including economically.

In short, nothing the United States does or does not do in this area of research is going to alter its pursuit. Hence our government, our scientists and our industries need to be aware of advances in DNA research wherever it occurs.

OVERSIGHT ACTIVITIES

Basic oversight activities of recombinant DNA research so far as regulation is concerned have been the responsibility of the Committee on Interstate and Foreign Commerce. They are described in Part 1 of this report, p. 34.

With regard to the basic research and science policy aspects of recombinant DNA activities, the subcommittee on Science, Research and Technology held extensive hearings during the period of March to September in 1977. More than 50 witnesses representing a wide variety of views were heard and much supporting data was submitted. Those hearings are available from the Committee on Science and Technology.

Hearings were also held after H.R. 11192 was sequentially referred to this committee, at which time Administration witnesses were heard as well as those representing the scientific community, industry and environmental groups.

OVERSIGHT FINDINGS BY THE COMMITTEE ON GOVERNMENT OPERATIONS

No statement of findings by the Committee on Government Operations has been received by the Committee on Science and Technology.

CONGRESSIONAL BUDGET ACT INFORMATION

No information pursuant to section 308(a) of the Congressional Budget Act of 1974 has been provided to the Committee by the Congressional Budget Office as of April 21, 1978.

ESTIMATE AND COMPARISON, CONGRESSIONAL BUDGET OFFICE

Pursuant to section 403 of the Congressional Budget Act of 1974 and to Clause 2(1)(3)(C) of Rule XI of the Rules of the House of Representatives, the report of the Congressional Budget Office on H.R. 11192 as amended by the Committee on Science and Technology following sequential referral from the Committee on Interstate and Foreign Commerce is as follows:

CONGRESSIONAL BUDGET OFFICE,
U.S. CONGRESS,
Washington, D.C., April 21, 1978.

Hon. OLIN E. TEAGUE,
Chairman, Committee on Science and Technology, U.S. House of Representatives, Washington, D.C.

DEAR MR. CHAIRMAN: Pursuant to Section 403 of the Congressional Budget Act of 1974, the Congressional Budget Office has prepared the attached cost estimate for H.R. 11192. This bill extends for two years the recombinant DNA experimental guidelines of the National Institutes of Health to all public and private recombinant DNA activities. It also provides for a study respecting research and technology involving genetic manipulation.

Should the committee so desire, we would be pleased to provide further details on the attached cost estimate.

Sincerely,

ALICE M. RIVLIN,
Director.

CONGRESSIONAL BUDGET OFFICE—COST ESTIMATE

APRIL 21, 1978.

1. Bill number: H.R. 11192.
2. Bill title: Recombinant DNA Act.
3. Bill Status: As ordered reported by the House Committee on Science and Technology on April 18, 1978.
4. Bill purpose: A bill to extend for two years the scope of the containment requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involiving genetic manipulation.
5. Cost estimate:

Projected costs

	Millions
Estimated authorization level:	
Fiscal year:	
1979	$2.42
1980	3.00
1981	0.77
1982	0
1983	0
Costs:	
Fiscal year:	
1979	2.23
1980	2.95
1981	1.01
1982	0
1983	0

The costs of this bill fall within budget function 550.

6. Basis for estimate: Enactment of H.R. 11192 would extend the National Institutes of Health regulatory and experimental guidelines for recombinant DNA research to all public and private recombinant DNA activities. Currently, only those activities funded by the NIH are covered. The bill also authorizes the creation of a commission for the study of research and technology involving genetic manipulation.

The assumptions made in estimating the authorization levels of H.R. 11192 were:

Approximately 200 newly covered laboratories will require 50 new regulatory inspectors (authorized for two years) at an average wage of $20,700 plus 70 percent for employee benefits, travel costs, and administrative expenses (all inflated in outyears by CBO's federal wage deflator); and

Creation of the study commission for the full 32 months authorized will require 10 members from outside the NIH at the stipulated GS–18 wage rate; since there is no precedent for estimating periodic increases in salary at this level, no assumption for future salary adjustments were made; an additional 60 percent for travel and administrative costs was added and inflated in outyears by CBO's federal wage deflator.

It is assumed that the estimated authorization levels will be fully appropriated at the beginning of each fiscal year. The costs are estimated on the basis of a current year spendout rate of .92 and a prior year balance spendout rate of .08.

While H.R. 11192 also provides for the imposition of penalties on laboratories with violations, HEW estimates that few, if any, penalties will be assessed.

7. Estimate comparison: None.

8. Previous CBO estimate: On March 23, 1978 CBO prepared a cost estimate on H.R. 11192 for the House Committee on Interstate and Foreign Commerce. The difference between the two estimates is that the earlier version of the bill did not specifically terminate the inspection program after two years and thus had inspection costs beyond 1981.

9. Estimate prepared by: John Nelson.

10. Estimate approved by:

C. G. Nuckols
(For James L. Blum,
Assistant Director for Budget Analysis).

COST AND BUDGET DATA

The following is the appropriate cost-of-legislation data, taken directly from Part 1 of this report:

Although the proposed legislation contains no line-item authorization of appropriations, the Department of Health, Education, and Welfare estimates that the following costs will be incurred by the Department in carrying out the functions assigned to it by H.R. 11192.

2-Year cost projections—H.R. 11192 Recombinant DNA Act

[Dollars in millions]

	1979	1980
Number of positions in HEW	50	75
Projected cost, Title I	$3.0	$4.5
Projected cost, Title II	.5	.5

These projections are based upon the current 200 laboratories now using recombinant DNA techniques, and the 300 projected by the end of fiscal year 1978. This number is expected to grow significantly in the near future.

The required staff positions include those involved in developing and conducting training programs for the approximately 1,500 scientists and technicians soon to be involved in recombinant DNA research, to handle paperwork involved with the registration of activities, and to assist the Secretary and the NIH Recombinant Advisory Committee in carrying out its duties to develop and review safety standards and then respond to inquiries from the scientific community regarding interpretation of the regulations and from the public regarding the safety and usefulness of recombinant DNA activities, and for inspectors and other general support staff.

The estimated cost of the study commission is listed separately.

INFLATION IMPACT

The following inflation impact statement is taken directly from Part 1 of this report:

> The committee anticipates that the enactment of H.R. 11192 will have a negligible impact on inflation in the biomedical research area and in Federal spending. As determined by the Congressional Budget Office, the cost to the government of expanding the scope of the NIH Guidelines governing recombinant DNA activity to encompass all such activity regardless of its funding source would be less than $3 million annually. In view of the potential hazards to the public health and the environment from improperly conducted recombinant DNA activities and the potential benefits to society which may derive from such activities, the minimal increases in expenses which may accrue to entities engaged in recombinant DNA activities in connection with compliance with the requirements of the proposed legislation are wholly appropriate.

COMMITTEE RECOMMENDATION

A quorum being present, the bill was ordered reported by the Committee on April 18, 1978, by a vote of 24 ayes, 4 nays, and 12 not voting.

ADMINISTRATION VIEWS

The views of the Administration on H.R. 11192, as reported by the Committee on Interstate and Foreign Commerce, were presented during hearings by the Subcommittee on Science, Research and Technology on April 11, 1978, by Dr. Donald S. Fredrickson, Director,

National Institutes of Health, and by Dr. Gilbert Omenn, Deputy Director, Office of Science and Technology Policy. Both witnesses recommended passage of the legislation.

A portion of Dr. Fredrickson's testimony follows:

> I am pleased to appear before this subcommittee today to testify on behalf of the Department on the Recombinant DNA Act (H.R. 11192) as reported by the Committee on Interstate and Foreign Commerce.
>
> The Department favors enactment of H.R. 11192 because this measure offers the most promising solution available for establishing national standards for the use of recombinant DNA techniques.
>
> Congressman Harley Staggers, Chairman of the Interstate and Foreign Commerce Committee, and Congressman Paul Rogers, Chairman of the Subcommittee on Health and the Environment, are to be commended for working effectively to develop an interim, two-year bill that provides for sensible regulation and public oversight. Your Subcommittee, Mr. Thornton, has also done an outstanding public service in the care and deliberation provided this most important research area in your extensive hearings over the past two years.
>
> H.R. 11192 reflects new scientific information and administrative developments since the release of the NIH Guidelines in June 1976 as do the revisions to the Guidelines proposed to me in September 1977 by the Recombinant DNA Molecule Program Advisory Committee (RAC).

DISSENTING VIEWS OF HON. MIKE McCORMACK ON H.R. 11192, THE "RECOMBINANT DNA ACT"

As it is now written, H.R. 11192 troubles me deeply. I believe the legislation regulates, unwisely, an essential area of pure research just when its potential for benefit to mankind is being realized; and I feel it sets a dangerous precedent for the regulation of scientific research in the absence of conclusive, or even demonstrated, significant danger.

It is ironic that this bill has resulted not from the threat of any epidemic or ecological disaster. Instead, it is an over-reaction to restraints placed on themselves by responsible scientists whose ethical standards prompted them to anticipate and guard against the mere possibility of danger from the recombinant DNA research technique. Through the NIH guidelines, these scientists imposed restrictions on themselves. After doing so, sensational stories appeared in the popular media, greatly exaggerating an illusory imminent danger. This led us down a road, paved with good intentions, to a bill through which we will attempt to regulate, by law, the conduct of recombinant DNA research.

It is ironic also that the law will be almost meaningless to anyone really intent upon doing DNA research outside established limits. The law is almost impossible to enforce in such instances, because such research can be made almost impossible to detect.

The same scientists who conceived the possibility of the danger of the recombinant DNA research have investigated the subject further and are now concluding that hazards are much less likely than they originally suspected. I quote Dr. David Baltimore, Nobel Prize Winner, in testimony before the Subcommittee on Science, Research and Technology, March 30, 1977:

> I was one of a group of scientists who, in 1974, first drew attention to the potential problems inherent in the manufacture and study of recombinant DNA molecules. . . . I am today much less concerned about hazards than I was.

Dr. Roy Curtiss, Professor of Microbiology, in a letter to Hon. Ray Thornton, April 12, 1977:

> [In 1974 I] suggested a voluntary cessation of essentially all recombinant DNA research until "potential biohazards can be assessed and means to cope with them established." . . . Since August, 1974 I have taken four actions, some of which have caused me to become far less apprehensive about recombinant DNA molecule research. . . . I am, however, extremely concerned that, based on fear, ignorance and misinformation, we are about to embark on over-regulation of an area of science.

Dr. Philip Handler, President, National Academy of Sciences, in testimony before the Subcommittee on Science, Research and Technology, April 11, 1978:

> The unusual history of this subject has laid upon those who would conduct this research the strange burden of offering a postive proof of "safety", when the extraordinary risks they must show not to exist are entirely imaginary in the first instance.

Not only are the risks of this research now considered to be too small for meaningful measurement, but there is general agreement that the benefits of recombinant DNA research are great. Again I quote "Science Policy Implications of DNA Recombinant Molecule Research." Report prepared by the Subcommittee on Science, Research, and Technology, U.S. House of Representatives, March 1978, page vii:

> Immediate benefits of recombinant DNA research appear to be more imminent than the risks which have been hypothesized."

Dr. Maxine Singer, Head, Section on Nucleic Acid Enzymology, National Cancer Institute at an NAS Forum: Research with Recombinant DNA, March 7, 1977:

> The promise of the (recombinant DNA) method for the preparation of useful and otherwise unobtainable quantities of specific DNA fragments or genes is an established fact.

For example, the gene for producing a type of animal insulin has already been introduced into micro-organisms by recombinant DNA techniques. The potential to produce human insulin, needed by diabetics, by recombinant DNA techniques is great.

A Dangerous Precedent

To my knowelge, this bill represents the first case of the regulation of basic scientific inquiry, using the Interstate Commerce clause, and in an area with no proven hazard. The concept of "proscribed knowledge" is completely alien to the United States. Freedom of inquiry is as indispensable as freedom of speech, and this bill sets the precedent of limiting freedom of inquiry when the need for such action has not been demonstrated.

Federal Pre-emption

I support portions of section 106, which provides that states and localities cannot regulate recombinant DNA activities, except in certain cases. Indeed, many of my colleagues have indicated that they favor the bill only because this pre-emption section is included.

Frivolous Suits

Section 104 of H.R. 11196 is an open invitation to frivolous, time-consuming, cruel lawsuits. A well-known tactic used by certain groups to delay research and development is to bring suit in any court in the country which is known to be sympathetic to their stands. I know all my colleagues join me in disdaining the practice of "shopping around" for favorable courts, but I see the danger of this happening with en-

actment of section 104. This section would be much less open to abuse if it were changed to provide (i) that suit could be brought only in the judicial district where recombinant DNA activity was actually conducted and (ii) that any citizen who wanted to sue would have to post a bond (of perhaps $5,000), which would be forfeited if the court decided that the suit was frivolous, capricious, or was made either in bad faith or for harassment.

In closing, I ask my colleagues to guard against delaying, and perhaps even preventing, vital discoveries regarding recombinant DNA by over-hasty, though well-intentioned, action. A national statement concerning appropriate research methodology may, indeed, be desirable. However, unnecessary and dangerous roadblocks to research progress exist in this legislation; and dangerous precedents are set, especially impacting on freedom of inquiry. DNA research may provide blessings for millions of persons in the future. It will be done somewhere, with or without this legislation.

MIKE MCCORMACK.

Union Calendar No. 547

95TH CONGRESS
2D SESSION

H. R. 11192

[Report No. 95-1005, Parts I and II]

IN THE HOUSE OF REPRESENTATIVES

FEBRUARY 28, 1978

Mr. STAGGERS (for himself and Mr. ROGERS) introduced the following bill; which was referred to the Committee on Interstate and Foreign Commerce

MARCH 24, 1978

Reported (with amendments), sequentially referred to the Committee on Science and Technology for a period ending not later than April 21, 1978, for consideration of such provisions as fall within the jurisdiction of that committee under clause 1(r), rule X, and ordered to be printed

[Omit the part struck through and insert the part printed in italic]

APRIL 21, 1978

Reported from the Committee on Science and Technology with amendments and ordered to be printed

[Omit the part enclosed in black brackets and insert the part printed in boldface roman]

A BILL

To extend for two years the scope of the containment requirements and the requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SHORT TITLE

SECTION 1. This Act may be cited as the "Recombinant DNA Act".

FINDINGS

SEC. 2. The Congress finds that—

(1) research and other activities involving recombinant DNA will improve the understanding of fundamental biological processes;

(2) the knowledge gained from such research and other activities may be of great benefit to medicine and agriculture and may provide many other benefits to society;

(3) while no hazard has been demonstrated, uncertainties exist regarding the extent to which organisms or viruses containing recombinant DNA may present a risk of injury to health or the environment, and there [is] **may be** a risk that any such potentially hazardous organisms or viruses may spread quickly and without warning to persons, agricultural plants and products, and other items in or affecting commerce;

(4) the public interest requires that until the uncertainties regarding the potential hazards of organisms and viruses containing recombinant DNA are resolved, the health and welfare of the population of the United States be protected from such hazards, and commerce

in the United States is dependent upon such protection being provided; and

(5) to effectively accomplish such protection and consequently to effectively regulate commerce requires that any activity involving organisms or viruses containing recombinant DNA (whether a research or commercial activity) be subject to control.

TITLE I—INTERIM REGULATION OF RECOMBINANT DNA ACTIVITIES

DEFINITIONS

SEC. 101. For purposes of this Act:

(1) The term "DNA" means deoxyribonucleic acid.

(2) The term "recombinant DNA" means DNA molecules which—

(A) ~~have been formed by joining together DNA segments in a cell free system~~ *are formed by joining together DNA segments outside of living cells* and which have the capacity to enter a cell and to replicate in such cell either autonomously or after they have become an integrated part of such cell's genome; or

(B) are the result of a replication of the DNA molecules described in subparagraph (A).

(3) The term "recombinant DNA activity" means

the possession in a State of recombinant DNA by any individual or public or private entity and any activity (including research and transportation) undertaken in a State by any individual or public or private entity for the production of recombinant DNA.

(4) The term "public entity" includes any Federal, State, or local governmental entity.

(5) The term "Secretary" means the Secretary of Health, Education, and Welfare.

EXTENSION OF THE RECOMBINANT DNA GUIDELINES

SEC. 102. (a) (1) Except as provided under subsection (b) and section 107 (b) (2), during the period beginning on the tenth day after the date of the enactment of this Act and ending twenty-four months after such day, all recombinant DNA activities shall be carried out in accordance with—

(A) the requirements of sections II (entitled "Containment") and III (entitled "Experimental Guidelines") of the recombinant DNA research guidelines of the National Institutes of Health of the Department of Health, Education, and Welfare published in part II of the Federal Register for July 7, 1976;

(B) if such requirements are revised before the tenth day after the date of the enactment of this Act,

such requirements as so revised and published in the Federal Register; or

(C) if such requirements are revised under paragraph (2), such requirements as so revised.

(2) The Secretary may, by regulation, amend in any manner any of the requirements in effect under paragraph (1) if he determines that the requirements in effect after such amendment will be sufficient for the protection of health and the environment. A regulation promulgated under this paragraph shall be promulgated in accordance with section 553 of title 5, United States Code.

(3) Before the expiration of the ten-day period beginning on the date of the enactment of this Act, the Secretary shall take such action as may be necessary to publicize and make available the requirements described in paragraph (1), including the publication of such requirements in the Federal Register.

(b) The Secretary may, by order, exempt, under such terms and conditions as the Secretary shall include in the order, from the requirements of subsection (a)(1) any recombinant DNA activity which the Secretary finds does not present a significant risk to health or the environment. Each such order shall be published in the Federal

Register together with a statement of the basis for the order.

(c) (1) Each individual or entity which, on the *tenth day after the* date of the enactment of this Act, is responsible for the conduct of any recombinant DNA activity shall, in accordance with regulations promulgated under subsection (d) and before the expiration of ~~ninety days from the date of the enactment of this Act~~ *ten days from the date such regulations first take effect under such subsection,* report in writing to the Secretary—

(A) such individual's or entity's name, and

(B) a description of such activity and an identification of the place or places in which it is being conducted, and

(C) assurances satisfactory to the Secretary that such activity will be carried out in accordance with the applicable requirements of subsection (a) (1).

(2) Each individual or entity which is to be responsible for a recombinant DNA activity to be commenced during the period described in subsection (a) (1) shall upon the commencement of such activity report in writing to the Secretary, *in accordance with regulations promulgated under subsection (d),* such individual's or entity's name, a description of such activity, an identification of the place or places in which such activity is to be conducted, and assurances sat-

isfactory to the Secretary that such activity will be carried out in accordance with applicable requirements of subsection (a) (1).

(d) Before the expiration of the ninety-day period beginning on the date of the enactment of this Act, the Secretary shall issue proposed regulations for the administration of the requirements of this section and section 105 and **[**may**]** **shall** include in such regulations provisions for reporting and for local entities to assist in the administration and enforcement of the requirements of subsection (a) (1), **as well as provisions giving due consideration to the need for protection against improper or unwarranted disclosure of privileged, confidential, or proprietary information, trade secrets, and information held under patent rights.** Such proposed regulations shall be promulgated without regard to section 553 of title 5, United States Code, and shall take effect upon their publication in the Federal Register. After such publication of such regulations the Secretary shall give interested persons an opportunity to submit written data, views, or arguments on such regulations and may provide opportunity for the oral presentation of views and arguments. After consideration of the relevant matter presented, the Secretary shall, by order, make such revisions in such regulations as he determines appropriate.

~~(e) The National Environmental Policy Act of 1969~~

~~shall not apply with respect to any action taken by the Secretary under this title.~~

PROHIBITED ACTS AND PENALTIES

SEC. 103. (a) No person may—

(1) conduct any recombinant DNA activity in violation of any applicable requirement of section 102;

(2) move in violation of an order issued under section 105(c) any recombinant DNA or any other material subject to such order; or

(3) fail or refuse to—

(A) establish or maintain records,

(B) make reports or provide information, or

(C) permit entry or inspection,

as required by this ~~Act~~ *title* or any regulation promulgated under this ~~Act~~ *title*.

(b) (1) Any person who violates subsection (a) shall be liable to the United States for a civil penalty in an amount not to exceed $5,000 for each such violation. Each day such a violation continues shall, for purposes of this paragraph, constitute a separate violation of subsection (a).

(2) A civil penalty for a violation of subsection (a) [shall] **may** be assessed by the Secretary by an order made on the record after opportunity (provided in accordance with this subsection) for a hearing in accordance with section 554 of title 5, United States Code. Before issuing such an order,

the Secretary shall give to the person to be assessed a civil penalty under such order written notice of the Secretary's proposal to issue such order and provide such person an opportunity to request, within fifteen days of the date the notice is received by such person, such a hearing on the order.

(3) Any person who requested in accordance with paragraph (2) a hearing respecting the assessment of a civil penalty and who is aggrieved by an order assessing a civil penalty may file a petition for judicial review of such order with the United States Court of Appeals for the District of Columbia Circuit or for any other circuit in which such person resides or transacts business. Such a petition may only be filed within the thirty-day period beginning on the date the order making such assessment was issued.

(4) If any person fails to pay an assessment of a civil penalty—

(A) after the order making the assessment has become a final order and if such person does not file a petition for judicial review of the order in accordance with paragraph (3), or

(B) after a court in an action brought under paragraph (3) has entered a final judgment in favor of the Secretary,

the Attorney General shall recover the amount assessed (plus interest at currently prevailing rates from the date of the expiration of the thirty-day period referred to in paragraph (3) or the date of such final judgment, as the case may be) in an action brought in any appropriate district court of the United States. In such action, the validity, amount, and appropriateness of such penalty shall not be subject to review.

(c) If the Secretary determines, after providing reasonable opportunity for an oral hearing, that a person has violated subsection (a) in carrying out a project for which financial assistance was provided by a grant made under a program administered by the Secretary and from funds appropriated after the date of the enactment of this Act, the Secretary may, in his discretion, cancel such grant or withhold payments under such grant until he determines that such person will carry out such project in accordance with the applicable requirements of section 102.

INJUNCTION AUTHORITY; EMERGENCY PROCEDURE

SEC. 104. (a) The district courts of the United States shall have jurisdiction over civil actions to restrain any violation of section 103(a). Such a civil action may be brought in the United States district court for the judicial district where any act, omission, or transaction constituting

a violation of section 103 (a) occurred or wherein the defendant is found or transacts business. In any such civil action, process may be served on a defendant in any judicial district in which the defendant resides or may be found. Subpenas requiring attendance of witnesses in any such action may be served in any judicial district.

(b) The district courts of the United States shall have jurisdiction over any civil action brought (1) for the seizure or destruction of any recombinant DNA, or any material used in or produced by a recombinant DNA activity, which recombinant DNA or material was involved in a violation of section 103 (a) or presents or may present a significant risk to health or the environment or (2) for other appropriate relief to prevent its production or movement. Such civil action shall be brought in the district court of the United States within the jurisdiction in which such recombinant DNA or material is found.

INSPECTIONS

SEC. 105. (a) (1) For purposes of enforcement of the requirements of section 102, individuals designated as inspectors by the Secretary, upon presenting appropriate credentials and a written notice to the person in charge of the place to be inspected and after clearly informing him of their authority, are authorized to enter and inspect any place (in-

cluding any vehicle or other conveyance which may be used in the transportation of recombinant DNA) in a State in which a recombinant DNA activity is being conducted or in which the inspector has reasonable grounds to believe such an activity is being conducted. A separate notice shall be given for each such inspection, but a separate notice shall not be required for each entry made during the period covered by the inspection. Such an inspection (A) shall be made during the normal business hours (if any) of the place being inspected and in a reasonable manner, and ~~(E)~~ *(B)* may extend to relevant equipment, materials, containers, records, files, papers, processes, controls~~, facilities, and all other things in the place~~ *and facilities* bearing on whether a recombinant DNA activity is being conducted in accordance with the applicable requirements of section 102.

(2) Upon completion of any inspection authorized by paragraph (1) and prior to leaving the place inspected, the inspector shall give to the person in charge of such place a preliminary report which summarizes any condition or practice observed by the inspector which, in his judgment, indicates a violation of the requirements of section 102. The inspector shall also prepare a written final report of his findings and send it to such person within thirty days of the completion of the inspection.

(b) At the request of an inspector conducting an in-

spection under subsection (a), the person in charge of the place inspected shall provide such samples of—

(1) recombinant DNA in such place, or

(2) materials used in or produced by any recombinant DNA activity conducted in such place,

as the inspector may require to determine if the applicable requirements of section 102 are being complied with.

(c) If during an inspection conducted under subsection (a), recombinant DNA or any material used in or produced by a recombinant DNA activity which the inspector making the inspection has reason to believe is involved in a violation of section 103 (a) or presents a significant risk to health or the environment is found in the place inspected, such inspector may order the recombinant DNA or material detained (in accordance with regulations promulgated by the Secretary) for a reasonable period which may not exceed twenty days unless the Secretary determines that a period of detention greater than twenty days is required to institute an action under section 104 (b), in which case the Secretary may authorize a detention period of not to exceed thirty days. Any recombinant DNA or material subject to a detention order issued under this subsection shall not be moved by any person from the place at which it is ordered detained until—

(1) released by the Secretary, or

(2) the expiration of the detention period applicable to such order,

whichever occurs first.

(d) No individual designated by the Secretary to conduct an inspection under subsection (a) shall be required to obtain a search or inspection warrant from any judicial officer before entering any place to conduct such inspection.

(e) No individual who is engaged in or has a direct financial interest in a project involving a recombinant DNA activity may be designated by the Secretary to conduct an inspection under subsection (a) of such project.

EFFECT ON STATE AND LOCAL REQUIREMENTS

SEC. 106. (a) Except as provided in subsection (b), no State or political subdivision of a State may establish or continue in effect any requirement for the regulation of recombinant DNA activities.

(b) Upon application of a State or political subdivision of a State, the Secretary shall, by order promulgated after providing (in accordance with this subsection) notice and opportunity for an oral hearing on such application and after considering local conditions, exempt from subsection (a) of this section, under such conditions as may be prescribed in such order, a requirement of such State or political subdivision applicable to recombinant DNA activities if—

(1) the requirement is the same as, or more stringent than, a requirement under section 102(a); and

(2) the requirement is necessary to protect health or the environment.

A State or political subdivision which submits an application under this subsection shall be given an opportunity for an oral hearing on such application to be commenced not later than sixty days from the date the application is submitted. The presiding officer at such a hearing shall upon conclusion of the hearing make a written recommendation to the Secretary respecting approval of the application upon which the hearing was held.

(c) Within—

(1) sixty days of the conclusion of a hearing held on an application submitted under subsection (b), or

(2) one hundred and twenty days of the date the application was submitted,

whichever occurs later, the Secretary shall either approve or disapprove such application. The decision of the Secretary shall be in writing, shall, if a hearing was held on the application, contain the recommendation made by the presiding officer at such hearing, and shall include a complete statement of the reasons for the decision of the Secretary.

TRAINING AND STUDIES

SEC. 107. (a) The Secretary may conduct and support training in the safe handling of recombinant DNA.

(b) (1) The Secretary shall conduct or support on a continuing basis studies designed to assess the risks to health and the environment which may be presented by recombinant DNA activities.

(2) The Secretary may, by order, make the requirements of section 102 inapplicable, under such terms and conditions as the Secretary shall include in the order, to any study conducted or supported under paragraph (1). Each such order shall be published in the Federal Register together with a statement of the basis for the order.

RELATIONSHIP TO OTHER FEDERAL LAWS

SEC. 108. (a) This title shall not affect the authority of any Executive agency (as that term is defined in section 105 of title 5, United States Code) to regulate under any other Act recombinant DNA activities.

(b) In exercising any authority under this title, the Secretary, or any person acting on behalf of the Secretary or pursuant to this title, shall not, for purposes of section 4(b)(1) of the Occupational Safety and Health Act of 1970, be deemed to be exercising statutory authority to prescribe or enforce standards or regulations affecting occupational safety and health.

(c) No part of this title shall remain in effect beyond the end of the period specified in section 102(a)(1).

TITLE II—COMMISSION FOR THE STUDY OF RESEARCH AND TECHNOLOGY INVOLVING GENETIC MANIPULATION

SEC. 201. (a) There is established, **within the Department of Health, Education, and Welfare,** a Commission for the Study of Research and Technology Involving Genetic Manipulation (hereinafter in this title referred to as the "Commission").

(b) (1) The Commission shall be composed of thirteen members appointed by the **[**Secretary of Health, Education, and Welfare**]** **President.** The **[**Secretary**]** **President** shall select members of the Commission from individuals distinguished **[**in the fields of**]** **in such fields as** medicine, law, ethics, the biological, physical, and environmental sciences, philosophy, humanities, health administration, government, and public affairs.

(2) (A) Except as provided in subparagraph (B), members of the Commission shall each be entitled to receive the daily equivalent of the annual rate of the basic pay in effect for grade GS–18 of the General Schedule for each day (including traveltime) during which they are engaged in the actual performance of the duties of the Commission.

(B) Members of the Commission who are full-time

officers or employees of the United States shall receive no additional pay on account of their service on the Commission.

(C) While away from their homes or regular places of business in the performance of duties of the Commission, members of the Commission shall be allowed travel expenses, including per diem in lieu of subsistence, in the same manner as persons employed intermittently in the Government service are allowed expenses under section 5703 of title 5 of the United States Code.

(c) The Chairman of the Commission shall be selected by the members of the Commission from among their number.

(d) (1) The Commission may appoint and fix the pay of such staff personnel as it deems desirable. Such personnel shall be appointed subject to the provisions of title 5, United States Code, governing appointments in the competitive service, and shall be paid in accordance with the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates.

(2) The Commission may procure temporary and intermittent services to the same extent as is authorized by section 3109 (b) of title 5 of the United States Code, but at rates for individuals not to exceed the daily equivalent of the

annual rate of basic pay in effect for grade GS–18 of the General Schedule.

SEC. 202. The Commission shall—

(1) conduct a study of Federal policy regarding activities involving the genetic modification of organisms and viruses and include in such study an evaluation of—

(A) the interim controls in effect under title I of this Act, actions taken to carry out and enforce such controls, and the need for an expansion of the scope of such controls;

(B) the effect of non-Federal requirements on recombinant DNA research and the necessity for preemption of such requirements by Federal requirements;

(C) federally sponsored programs to assess [the risk to health and the environment] **such risks to health and the environment as may be** presented by recombinant DNA research; and

(D) federally sponsored basic and applied recombinant DNA research; and

(2) conduct a study of the long-term consequences of the development of a technology capable of accomplishing the genetic modification of organisms and viruses and include in such study—

(A) an evaluation of the anticipated applications of genetic manipulation technology to such areas as medicine, pharmacology, immunology, industrial fermentation, and agriculture; [and]

(B) a thorough consideration of the ethical, moral, social, economic, **environmental,** and political implications of the development and use of such [technology.] **technology, as well as the significance of lessons learned through recombinant DNA research and its allied science policy issues; and**

(C) a comprehensive assessment of the status and applications, achieved or anticipated, of genetic manipulation technology in other nations engaged in such activities.

SEC. 203. (a) The Commission shall in carrying out its duties under section 202 hold public hearings as appropriate.

(b) The Commission may secure directly from any department or agency of the United States information necessary to enable it to carry out its duties. Upon the request of the Chairman of the Commission, the head of such department or agency shall furnish such information to the Commission.

SEC. 204. (a) Not later than eighteen months after the date of the enactment of this Act, the [Secretary] **Commis-**

sion shall report to the Congress the preliminary results of the evaluation being conducted under paragraph (1) of section 202.

(b) Not later than thirty months after the date of the enactment of this Act, the Commission shall (1) complete the studies prescribed by section 202, and (2) on the basis of such studies, make recommendations to the Congress, the President, and the appropriate Federal agencies regarding such Federal action as the Commission determines should be taken to promote, regulate, or review activities involving the genetic manipulation of organisms or viruses.

(c) The Commission shall terminate within sixty days of the date upon which it has carried out subsection ~~(a)~~ *(b)*.

Union Calendar No. 547

95TH CONGRESS
2D SESSION

H. R. 11192

[Report No. 95–1005, Parts I and II]

A BILL

To extend for two years the scope of the containment requirements and the requirements of the experimental guidelines of the National Institutes of Health respecting recombinant DNA research to include all public and private recombinant DNA activities and to provide for a study respecting research and technology involving genetic manipulation.

By Mr. STAGGERS and Mr. ROGERS

FEBRUARY 28, 1978

Referred to the Committee on Interstate and Foreign Commerce

MARCH 24, 1978

Reported (with amendments), sequentially referred to the Committee on Science and Technology for a period ending not later than April 21, 1978, for consideration of such provisions as fall within the jurisdiction of that committee under clause 1(r), rule X, and ordered to be printed

APRIL 21, 1978

Reported from the Committee on Science and Technology with amendments and ordered to be printed

FOR RELEASE UPON DELIVERY

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON PATENT POLICY

BEFORE THE

SUBCOMMITTEE ON MONOPOLY AND ANTICOMPETITIVE ACTIVITIES

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

JUNE 26, 1978

Introduction

I am pleased to be with you today to discuss the National Institutes of Health's perspectives on patent policy. I will deal first with patent policy as it relates to biomedical research generally, and then discuss a specific patent policy issue--recombinant DNA inventions developed with the help of NIH funds.

General Department Patent Policy

Under current DHEW patent regulations, invention rights to discoveries developed under the Department's research support are normally allocated in either of two ways:

First, the Department may enter into an Institutional Patent Agreement (IPA) with a university or other nonprofit organization that has set up mechanisms for administering patents on inventions.

- In 1968, the present IPA's replaced agreements developed by the Department in the 1950's. These earlier agreements proved to be non-uniform and, in some instances, inconsistent. The legal basis for the establishment of the IPA program does not rest on specific statutory authority but rather on the general authority of the Secretary to prescribe regulations and set the terms and conditions for grants and contracts.
- The IPA offers the institution the first option to own all inventions made in performance of Department grants subject to a number of conditions deemed necessary to protect the public interest.

Detailed conditions are set forth for institutions to grant licenses, and a set of conditions for the distribution of royalties is included. Institutions must grant the Government a license to make the invention or have it made for Governmental purposes. Under patent law, the use of patents for research purposes is not an infringement, and ordinarily the invention may be used in research without payment of royalties.

- o There are 72 IPA's now being administered by the Department. The Department Patent Branch reports that 167 patent applications were filed under IPA's from 1969 through the fall of 1974. Approximately $24 million is committed by private industry to the development of inventions on the basis of licenses granted under these patents.

Second, for those institutions or organizations that have not entered into a patent agreement with the Department, a somewhat different procedure is followed: In this situation, determination of ownership generally is deferred until an invention has been made, at which time an institution may petition the Department for ownership of the invention or a license under the invention.

- o In the past, approximately 90 percent of all such petitions have been granted on the basis of a satisfactory plan proposed by the institution for developing or licensing. During the period from 1969 to the fall of 1974, the Department has reviewed 178 petitions for ownership from institutions not having IPA's and has granted

162 of them. The plans proposed by the institutions call for approximately $53 million to be invested by private industry for development under the licenses awarded through this mechanism. Since the review of the Department's patent policies has not yet been completed, it would be premature to comment on the GSA amendment to the Federal Procurement Regulations mentioned in your letter.

Patenting of Recombinant DNA Research Inventions

In June 1976, shortly before the release of the NIH Guidelines on recombinant DNA research, Dr. Robert M. Rosenzweig, Vice President for Public Affairs at Stanford University, sent me a letter asking NIH to review DHEW policies relating to the patenting of recombinant DNA research inventions. Dr. Rosenzweig noted that both Stanford and the University of California were applying for patent protection for recombinant DNA research inventions developed by their investigators under NIH support. However, in view of the intense public interest in this research generally, the two universities felt the need for a formal advisory opinion by NIH on the patenting of recombinant DNA inventions developed under NIH grants or contracts. A number of other universities indicated similar interest in obtaining the official views of NIH.

Prior to making an official pronouncement of DHEW-NIH policy with respect to patenting of recombinant DNA research inventions, NIH decided to solicit comments from a broad range of individuals and institutions including the scientific community, the public and the private sector.

The views of commentators were solicited on excluding recombinant DNA research inventions from IPA's, so that patents would be granted only for dedication to the public. Possible approaches include the following:

Recombinant DNA research inventions could be excluded from the IPA's. Alternatively, the IPA could require institutions filing patent applications for recombinant DNA research inventions to dedicate all issued patents to the public. Finally, a condition could be added to the institutional patent agreement requiring institutions to assign to DHEW all recombinant DNA research inventions developed under Department support. The Department, as the patent holder, could either dedicate the patent to the public or pursue licensing, with appropriate conditions attached. There was little support among commentators for any of these options. They preferred to have DNA research inventions covered under the IPA's.

Commentator views were also solicited on the possibility of extending NIH Guidelines to the private sector by requiring adherence to the Guidelines through IPA's. The commentators generally supported this extension of Guidelines to private industry through use of IPA's. However, a number pointed out that use of the patent system to achieve compliance with the Guidelines was at best a make-shift solution, because of the difficulty in exercising regulatory control through the patent process.

A review and analysis of comments received on the question of patenting recombinant DNA inventions were completed in December 1976 and referred to the Federal Interagency Committee on Recombinant DNA Research for their attention.

The Interagency Committee, convened by the Secretary of HEW with the approval of the President, serves as a forum to review Federal policy on recombinant DNA issues. It provides coordination among the agencies on recombinant DNA activities and makes administrative and legislative proposals when appropriate.

On the Committee are representatives of all Federal Departments and agencies that support or conduct such research or might have regulatory authority over it.

A number of the agency representatives referred the analysis to their patent counsels. Among agencies commenting were the National Science Foundation, the Defense Department, the Department of Agriculture, the Energy Research and Development Administration, and the Department of Justice.

All agencies on the Committee except Justice agreed that recombinant DNA research inventions should be handled on the same terms as other inventions under IPA's. The Department of Justice believed that, because of the great public interest in this field, ownership of any invention stemming from Government-sponsored recombinant DNA research should be held by the U.S. Government.

One question remains: whether the subject of the patentable processes (specifically recombinant DNA techniques) is of such a distinctive nature that financial return to the inventors should be denied. This position had few advocates among the commentators. There are no compelling economic, social, or moral reasons to distinguish these inventions from others involving biological substances or processes that have been patented, even though developed partially or wholly with public funds. Such inventions include vaccines for rubella and rabies, treatments for herpes infections of the eye, and treatments for uremia. The argument that commercial development of these inventions based on patent protection assures maximum benefits to the public applies as well to the putative benefits of recombinant DNA inventions.

It is recognized that Federal patent policies are under extensive review by the Executive Branch and the Congress. This may lead to actions that could affect the administration of Institutional Patent Agreements generally and the conditions for recombinant DNA research inventions specifically.

It is my decision, however, that recombinant DNA research inventions developed under DHEW-NIH support should, at least for the present, continue to be administered within current DHEW patent agreements with the universities. But such agreements should be amended to ensure that, in any production or use of recombinant DNA molecules, the licensees will comply with the physical and biological containment standards set forth in the Guidelines. This decision was announced in March 1978,

with the concurrence of the HEW Office of General Counsel and the Public Health Service. Mr. Chairman, I would like to submit for the record my decision, the supporting analyses, and all of the comments received. These documents are compiled in Recombinant DNA Research Volume 2, Documents Relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules," June 1976-November 1977.

In response to the question in your letter, the Harvard investigators who reported on inducing a bacterium to produce insulin were funded by the NIH, and the university has filed a patent application under its IPA. Several other patent applications have been filed in the recombinant DNA area. I am enclosing a list for the record, Mr. Chairman.

Also, in your letter of invitation you asked me to comment on the fact that in March 1977 NIH introduced the phrase "patentable material" into its standard justification for closing peer review meetings pursuant to exemption 4 of the Federal Advisory Committee Act (FACA). The Federal Advisory Committee Act used to include the same exemptions contained in the Freedom of Information Act (FOIA).

Passage of the Government in the Sunshine Act, effective in March 1977, eliminated the Federal Advisory Committee's use of FOIA exemptions and substituted the Sunshine Act's exemptions as reasons for closing advisory committee meetings. This change did not alter NIH's basic approach in using exemption 4. While the Sunshine Act became the source of exemptions in place of the Freedom of Information Act, exemption 4 is

essentially the same in both statutes. However, we took the opportunity occasioned by the passage of the Sunshine Act to change the standard language used by NIH in citing exemption 4. In so doing, we shifted to the current format to clarify the grounds on which meetings could be closed. In making this language change, no substantive shift from the prior practice was intended.

In fact, NIH's operating instructions to its Committee Management Officers, as revised in light of the Sunshine Act, continue to provide that exemption 4 is not to be used in situations when it is evident in advance that information covered by the exemption will not come up for discussion.

Mr. Chairman, that concludes my statement. I would be pleased to respond to any questions or comments you may have.

[COMMITTEE PRINT]

95TH CONGRESS
2d Session
SENATE

RECOMBINANT DNA RESEARCH AND ITS APPLICATIONS

OVERSIGHT REPORT

BY THE

SUBCOMMITTEE ON
SCIENCE, TECHNOLOGY, AND SPACE

OF THE

SENATE COMMITTEE ON
COMMERCE, SCIENCE, AND TRANSPORTATION

together with

MINORITY VIEWS

AUGUST 1978

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LETTER OF TRANSMITTAL

Hon. HOWARD CANNON,
Chairman, Committee on Commerce, Science, and Transportation, U.S. Senate, Washington, D.C.

DEAR MR. CHAIRMAN: I am submitting herewith an oversight report by the Subcommittee on Science, Technology, and Space on the regulation of recombinant DNA research and its applications, together with the minority views of Senator Harrison Schmitt, ranking minority member. The subcommittee's findings and recommendations for the regulation of recombinant DNA activities are based in the first instance on its hearings on November 2, 8, and 10, 1977. During these hearings 27 witnesses discussed the benefits and possible risks of research using recombinant DNA techniques, issues of scientific freedom and responsibility, the administration of the National Institutes of Health research guidelines, and the need to extend these controls to privately sponsored research projects.

The report is also the first systematic effort to examine the issues that are likely to arise in the regulation of future large-scale commercial applications of recombinant DNA techniques. Following the subcommittee's hearings, opinions were requested of the relevant Federal regulatory agencies, the Congressional Research Service, and several of the witnesses. Analysis of these views and recommendations are included in part II of this report; related documents are found in the appendix.

The subcommittee is grateful for the assistance of Dr. James M. McCullough, Senior Specialist in Life Sciences, and Donna C. Parratt, Legislative Attorney, both of the Congressional Research Service, and to Dr. Bernard Talbot, Office of the Director, National Institutes of Health, who reviewed the technical material in the report.

Sincerely,

ADLAI E. STEVENSON,
Chairman,
Subcommittee on Science, Technology, and Space.

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SUMMARY OF FINDINGS AND RECOMMENDATIONS

The subcommittee finds that the use of recombinant DNA techniques is rapidly increasing scientific understanding of basic biological phenomena and is likely to have important applications in the manufacture of drugs and industrial enzymes, waste treatment, production of food crops, and treatment of genetically related diseases. In the absence of confirmed hazards, the benefits that have been and may be derived from research with recombinant DNA molecules justify its continuation and support by the Federal Government and the private sector.

As a result of apprenhensions about its effects on health and the environment, however, recombinant DNA research has been subject to various restrictions, principally the 1976 guidelines governing research supported by the National Institutes of Health. Recent scientific data indicate that permissible experiments employing NIH-approved host organisms and vectors do not pose significant risks to laboratory workers, the public, or the environment. Uncertainty remains, however, about the safety of experiments with other materials and about the hazards that may be associated with future uses of the technology, including the large-scale production of organisms with recombinant DNA and their release into the environment for presumably beneficial purposes. These uncertainties, which will be resolved over the course of years, justify continued exercise of caution in both research and commercial applications of recombinant DNA techniques.

Current Federal guidelines requiring the use of precautionary measures are nevertheless deficient in several respects. The National Institutes of Health lack authority to monitor and enforce compliance with the guidelines by those engaged in research supported by private funds or other Federal agencies. It is doubtful, in any case, whether enforcement by the principal Government sponsor of recombinant DNA research is appropriate and will be effective. As presently written and administered, the guidelines do not fully insure the accountability of institutions and investigators. The relationship between Federal and State and local government regulations is unsettled and controversial. Procedures are unclear for revising the standards to reflect new scientific evidence relating to the possible hazards or absence of hazards associated with recombinant DNA research. The standards do not purport to deal with its prospective commercial applications and the concerns they raise.

Research

The subcommittee believes that the NIH standards should be applied to all recombinant DNA research regardless of its locale or sources of financial support. This can be accomplished by legislation

or possibly by administrative action under the authority of section 361 of the Public Health Service Act, which in the past has been used to control a variety of infectious and some noninfectious agents. The Secretary of HEW has expressed a preference for a specific legislative mandate. If Congress does not act on legislation, however, the Secretary should reconsider using the authority of the Public Health Service Act.

In either case, recombinant DNA should be defined as broadly as it is defined in the current NIH guidelines. It is also assumed that the standards for research will be similar if not identical to those required by the guidelines, which prohibit certain presumably dangerous experiments, require certification of the safety of host-vector systems, and prescribe physical and biological containment measures for the conduct of permissible experiments. The administering agency should have authority to revise the standards periodically, provided that there is opportunity for public comment and examination of the supporting data. There should also be authority to exempt from the requirements those classes of experiments that are shown to pose no significant risk to health or the environment and to waive the ban on particular experiments whose results are necessary to assess the risks of recombinant DNA research. In all of these actions the administrator should have the advice of a group of qualified scientists and laypersons, including members of the present NIH Recombinant DNA Molecule Program Advisory Committee.

The subcommittee recommends that institutions be certified to conduct recombinant DNA research. The certificate should be conditional upon the appointment and conduct of an institutional biosafety committee to approve research projects, certify laboratory facilities, provide for the training of laboratory workers and researchers, monitor the health of persons exposed to recombinant DNA materials, and keep such records and make such reports as are deemed necessary. For informational purposes, research projects should be registered in advance with the administering Federal agency. Because it would be inappropriate to disqualify an entire institution in the event of violations by a single or a few researchers, the Federal administrator should have authority, subject to procedural safeguards, to suspend the activities of such offenders for a period of time. In cases of serious knowing violations of the standards, civil penalties would be appropriate. Federal agencies sponsoring or conducting recombinant DNA research would retain authority to terminate funding of activities being conducted in violation of the standards. Certification, registration, inspection and reporting responsibilities should be delegated to the Center for Disease Control or another agency apart from NIH. To protect the confidentiality of trade secrets and patentable inventions, there should be a procedure for notifying and consulting with researchers, both publicly and privately funded, prior to disclosure of information by the Government.

The subcommittee recommends that legislation contain a limited preemption provision barring States and communities from prohibiting recombinant DNA research or imposing physical and biological containment requirements exceeding the Federal standards. However,

the Federal agency should be empowered to waive Federal preemption if a State or local government presents convincing reasons in support of stricter standards. States and localities should also be permitted to take other actions to assure their citizens that the Federal standards are being observed. While this limited preemption could not be accomplished under section 361 of the Public Health Service Act, the subcommittee's recommendation does not differ significantly from the status quo; few communities have imposed requirements exceeding the standards incorporated in the NIH guidelines. Legislation should not expire earlier than 3 years after its enactment in order to have sufficient time to assess the effect of and need for Federal standards.

Commercial applications

The subcommittee recommends maximum use of existing statutory authorities to require premanufacturing and premarketing review, testing, quality controls in manufacture, and safe transportation and disposal of recombinant DNA products and materials. For example, regulation of pesticidal applications should remain with the Environmental Protection Agency, employee health and safety with the Occupational Safety and Health Administration, drugs and related products with the Food and Drug Administration, and transportation of materials with the Department of Transportation.

The Environmental Protection Agency has authority under the Toxic Substances Control Act to regulate uses of recombinant DNA molecules not covered by other statutes. The relatively few weaknesses in these laws should be corrected by use of supplementary authorities such as section 361 of the Public Health Service Act and the plant and animal quarantine laws or by amendment.

To avoid conflicting regulation by different agencies of recombinant DNA activities, there will be a need for effective coordination; memoranda of understanding or an Executive order should be used to clarify agencies' responsibilities. These agencies should also receive additional funds and personnel to carry out their duties, depending upon the rate of development of recombinant DNA technology.

INTRODUCTION

The ability to recombine DNA molecules of different organisms holds the promise of important benefits, both intellectual and material. Theoretically, it may also create hazards to human beings or the environment or interfere in unpredictable ways with hereditary processes. Exchanges of genetic material among organisms occur naturally, and no illnesses or other adverse effects have been associated with recombinants produced in the research laboratory. Nevertheless, many scientists and laypersons believe that the degree of uncertainty and the magnitude of the hypothesized risks justify restricting the use of recombinant DNA techniques.

American society, however, places great value on scientific and academic inquiry and has been reluctant to limit their freedom. Even where the risks of research are known, Government has not always acted to reduce them. The Atomic Energy Act imposes controls on the scientific use of radioactive substances, and restrictions are placed on the use of human subjects in experimentation; but pathogenic organisms and toxins have long been used in research, largely without Government interference or serious adverse effects on public health. Regulation of recombinant DNA technology represents public control of research procedures whose scientific utility is proven, whose social benefits may be significant, and whose dangers are not evident.

Understandably, Congress has found it difficult to reach an acceptable legislative resolution of these issues. The difficulty arises from conflicting values and perceptions in the absence of long experience with recombinant DNA techniques and knowledge of their effects. Legislative attempts to protect public health and the environment without impeding further research and development have met with criticisms from both sides of the controversy. Some charge that the proposed controls are inadequate; others argue that they represent unwarranted and dangerously restrictive Government control of scientific investigation.

Pursuant to its jurisdiction over "science, engineering, and technology research and development policy," the Subcommittee on Science, Technology, and Space held 3 days of hearings on recombinant DNA research in November 1977; the subcommittee later examined the possible commercial applications of this technology. These inquiries reflect the subcommittee's concerns both about the protection of public health and the environment and about the implications of regulation for scientific research and development activities generally. While the former concern dictates caution in the conduct of recombinant DNA research, the latter concern dictates care in the design and implementation of restrictions on it. The following oversight report presents the subcommittee's conclusions and recommendations for legislative and executive action.

Initial concerns

Scientists involved in genetic and biomolecular research first suggested that there might be risks associated with recombinant DNA experimentation. In a series of conferences and public statements beginning in 1973, they stressed the need to obtain more factual evidence concerning these hypothetical risks and the need, in the meantime, to devise a strategy to protect laboratory workers, the public, and the environment. Most scientists willingly agreed that they should exercise great caution during this period of risk investigation and assessment.

Reflecting these concerns, the National Institutes of Health in July 1976 published guidelines governing all recombinant DNA research supported with NIH funds. The NIH guidelines prohibited certain experiments that were presumed to be dangerous and prescribed procedures for others that might create unintended hazards. Other Federal agencies subsequently adopted these rules, and the handful of private firms engaged in recombinant DNA experimentation voluntarily agreed to observe them. Officially, however, the guidelines did not cover privately funded activities; only Government-supported research projects were subject to review for compliance and penalties for violations.

As the scientific community developed what the majority of researchers considered responsible self-controls, public debate ensued over the relative benefits and risks of recombinant DNA research. In addition to fearing that pathogenic organisms might be created in the laboratory and released into the environment, many persons were deeply concerned about tampering with the natural genetic order. Much of this debate took place outside of Washington, D.C., in universities and before State legislative bodies and city councils. Several communities extended the NIH guidelines to privately supported research activities; but more restrictive regulations were considered and, in a few instances, were adopted. At this juncture many of the same scientists who raised the question of potential dangers expressed apprehension that excessive regulation and differing State and local standards would have a chilling and disruptive effect on scientific investigation.

During this period (1974–77) additional evidence relating to the concerns about recombinant DNA research began to accumulate. The results pointed to a high level of safety associated with the use of certain laboratory-developed experimental organisms, such as the K–12 strain of the bacterium *Escherichia coli*, although other presumed risks were still acknowledged. Some experiments indicated that many of the DNA recombinations initially believed by scientists to be "novel" were, in effect, only laboratory-controlled duplications of events that occur in nature. There were also reports of advances in the use of recombinant DNA technology to produce mammalian hormones.

For many scientists, although not all, this new evidence made it less necessary and desirable for the Federal Government to regulate conduct of the research. Revisions of the NIH guidelines to reflect recent scientific findings were proposed. By mid-1977 these developments, taken together, raised doubts about the wisdom of the type of legislation previously contemplated.

Legislative activity

James Watson, co-recipient of the Nobel prize for characterizing the structure of the DNA molecule, first called the attention of Congress to the likely development of new techniques in genetic research during a 1971 hearing before the House Committee on Science and Technology. Four years later the Health Subcommittee of the Senate Committee on Human Resources held hearings on genetic engineering. During the past 3 years, nine separate sets of hearings have been held by committees of the House and Senate.

The Carter administration sent draft legislation to Congress in early 1977. Several Senators and House Members introduced their own bills, and it seemed all but certain that Congress would complete action on recombinant DNA legislation prior to the July 4 recess. The Human Resources Committee reported S. 1217, introduced by Senator Edward Kennedy of Massachusetts, in July 1977. In early August, Senator Gaylord Nelson of Wisconsin introduced to S. 1217 an amendment in the nature of a substitute which followed the basic regulatory approach contained in the legislation developed by Representative Paul Rogers of Florida, chairman of the Health and Environment Subcommittee of the House Committee on Interstate and Foreign Commerce. In September, Senator Adlai Stevenson of Illinois, chairman of the Subcommittee on Science, Technology, and Space, suggested in a Senate speech that the recent scientific developments and the reassessments then being conducted by the National Intitutes of Health and the Carter administration made it desirable to postpone final legislative action until 1978. In the meantime Senator Harrison Schmitt of New Mexico, ranking minority member, requested that the subcommittee hold hearings on the issue.

In these circumstances, the subcommittee conducted 3 days of hearings on November 2, 8, and 10, 1977. Twenty-seven witnesses (listed in the appendix) testified. Among the questions discussed at these hearings were the following:

> What are the actual and potential benefits of recombinant DNA research and technology? How long will it take for the potential benefits to be realized?
>
> What hazards must be taken into account in devising regulations for recombinant DNA research and technology? What has scientific investigation disclosed concerning the hypothetical risks that initially concerned many scientists?
>
> What approach should underlie regulation of recombinant DNA research in the public and private sectors? Should there be common regulatory procedures covering both publicly funded and privately funded research? Do the NIH guidelines provide a basis for regulation of the private sector?
>
> Do existing Federal statutes provide a basis for regulating recombinant DNA research and technology conducted with private funds?
>
> Should there be uniform standards for research in all localities of the country? How can the concerns of State and local populations for public health and environmental protection be accommodated?

How can the Government insure the health and welfare of the public without intruding unnecessarily on the freedom of scientific inquiry?

When is the commercial application of recombinant DNA technology likely to begin? Do adequate Federal regulatory safeguards exist to protect human beings and the environment from the potential hazards associated with large-scale use of this technology?

In addition to the testimony at the November hearings, the subcommittee received extensive supplementary material from witnesses and others. Federal agencies perceived to have any role in supporting or regulating recombinant DNA research or technology were asked whether existing statutes could provide an adequate basis for Federal controls. A list of those who submitted written statements and responses to the subcommittee's inquiries are found in the appendix.

PART I—PRINCIPAL FINDINGS

Actual and Potential Benefits

THE TECHNIQUE AND ITS SCIENTIFIC SIGNIFICANCE

In recombinant DNA research, specific sections of a DNA molecule are extracted from an organism or constructed biochemically and then inserted into another DNA sequence. The so-called recombinant DNA molecule is then introduced into a host organism where it can survive and replicate in cell division. This technique of artificial genetic exchange may be performed with organisms that commonly exchange DNA or with genetic material from two very dissimilar organisms, such as a mammal and a bacterium.

The host organism used in the vast majority of experiments is a strain of the common bacterium *Escherichia coli.* In addition to its single large chromosome containing DNA, *E. coli* has one or more independently replicating smaller loops of DNA known as plasmids. The plasmids are relatively easily isolated from the bacteria and broken open by restriction enzymes. The foreign DNA is linked to the plasmid DNA and its circular form restored. The plasmid "vector" is then returned to the whole cell bacterium where it can resume replication, duplicating not only the native DNA sequence but also the foreign one. If, in addition, the foreign DNA molecule carries with it the mechanism which regulates its expression, it may produce the protein or other chemical for which it codes.

The development of this technique is widely regarded as a major advance in the biological sciences, both as a means of studying basic biological phenomena and as a technology with numerous beneficial applications. In his testimony to the subcommittee, Philip Handler, President of the National Academy of Sciences, described DNA recombination as a research tool of "extraordinary power" for understanding the structure and functioning of the genetic apparatus. He referred to a recent report, "The Risks and Benefits of Recombinant DNA Research Performed Under the NIH Guidelines" (November 1, 1977), by a panel convened by the National Research Council of the Academy, which cited work using preselected genes of various animals including fruit flies, frogs, and sea urchins. The report states that "the distribution of likely regulatory sequences along cellular chromosomes has been mapped, using cloned recombinant DNA segments, and has suggested an unexpected mobility of genes." Similar experiments are being done with plants. These and other developments are contributing to an understanding of the general principles of chromosomal organization, genetic regulation, and inheritance as well as genetic abnormalities.

According to Stanford Professor Stanley Cohen, in a letter to the subcommittee, more than 250 scientific investigations involving recom-

binant DNA have been published in the last 4 years. The National Institutes of Health, which has supported a large proportion of this research, is presently funding approximately 375 proejcts.

APPLICATIONS OF RECOMBINANT DNA TECHNOLOGY

Laboratories supported by both public and private funds are already working on possible applications of the technique in medicine, industry, and agriculture. Officials of the Pharmaceutical Manufacturers Association reported that three member firms are engaged in recombinant DNA research and three others are financing experiments being conducted in universities. PMA President Joseph Stetler cautioned that "a substantial amount of basic research will be necessary before the feasibility of recombinant DNA technology in commercial development can be determined with any degree of accuracy." Researchers and knowledgeable observers have, nonetheless, become increasingly optimistic in recent months. Several witnesses predicted that at least a few commercial uses of recombinant DNA will be developed within 5 or 10 years.

Products from micro-organisms

The application most often mentioned involves the propagation of large quantities of microorganisms with recombinant DNA for the production of a useful product, followed by the extraction of the product and destruction of the cell material and other byproducts. This procedure may become a source of animal proteins such as antibodies, blood-clotting factors, human hormones, and antigens or of industrial enzymes for fermentation and other biochemical manufacturing processes. Although unproven, it is hoped that the technique will be more efficient than present laborious or costly methods of synthesis and extraction, provide a source for products in short supply, or produce substances with entirely new commercial uses.

There has been notable progress in the development of this process. In the spring of 1977, researchers at the University of California Medical School at San Francisco successfully introduced and cloned in *E. coli* bacteria the gene which codes for the production of insulin in rats, although the material lacked the mechanism which controls the production of insulin. More recently, a team of Harvard University and Joslin Diabetes Foundation scientists achieved the synthesis of rat proinsulin, the precursor protein. In the opinion of William Rutter, a member of the San Francisco research group, it will be possible to produce human insulin in bacteria inexpensively and in greater quantity than is now available. As an added benefit, the insulin otained in this manner may not induce production of antibodies in diabetic patients.

Another accomplishment within the past year by scientists at UCSF, the City of Hope Medical Center, and the Salk Institute involved the incorporation into *E. coli* of the gene for the mammalian hormone somatostatin, accompanied by the genetic material necessary for expression. In this case, the gene was synthesized chemically since it has not been isolated from the exceedingly complex mammalian DNA sequence. A small amount of somatostatin was obtained from the bacterial culture. Somatostatin is secreted by the hypothalamus and acts

as an inhibitor to the production of glucagon and insulin and to the pituitary gland's release of hormones regulating body growth.

Roy Curtiss of the University of Alabama noted in his testimony that modification of the microorganism so that gene expression occurs is only the first of several difficulties that will be encountered in producing hormones commercially.

Second will be to prevent the microorganisms from degrading proteins which are nonfunctional, and the presence of a hormone would seem to be in that category. Third will be to allow the microbial host to secrete the hormone into the culture medium to facilitate its recovery, free from bacterial contamination. Fourth, in addition to these essential modifications of the microbial host-vector system, it would be highly desirable to have the microorganism adapted for use in fermentation technology and thus grow on an inexpensive medium with maximum yields of hormone and minimum yields of microbial cell mass.

Nevertheless, Ronald Cape, president of Cetus Corp. of California, suggested that some nonmedical products could be available in a year or two if there are adequate markets for them.

Other applications

More speculative uses of recombinant DNA include the release of the modified host cell into the environment for some specific purpose such as the conversion of organic material in sewage treatment, the oxidation of petroleum spills, or improvement in the nitrogen-fixing capability of plants. In all of these examples the intention would be to establish the recombinant organisms in a natural environment as substitutes for organisms which perform the same functions but less efficiently. Alternatively, it has been suggested that a modified vector, probably a virus, could be used to infect plants or animals in order to increase the photosynthetic capability of plants, destroy insect pests, or produce some other desired genetic change. The most dramatic example would be the injection into human beings of a virus capable of correcting disease-causing genetic defects.

Service industry

If research and development with recombinant DNA progress as the subcommittee's witnesses expect, it may become profitable for commercial firms to supply specialized products to academic and commercial laboratories. These include not only restriction enzymes but also selected or general DNA segments, vectors with precise specifications, and even organisms containing recombinant DNA. Such material is already routinely exchanged among research laboratories. More than likely, the volume of shipments would not be large, for the naked DNA would be inserted into a small number of vectors, the vectors incorporated into microorganisms, and the organisms propagated in quantity in the research or industrial laboratory.

Potential Hazards

GENERAL CONCERNS

The ability to transfer genetic information across biological barriers previously considered to be blocked has raised three distinct concerns: first, that some new pathogenic microorganism might be created, escape from the laboratory, and prove dangerous to man or the

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environment; second, that research may ultimately lead to genetic manipulation of human beings; and third, that interference with natural evolutionary processes may do incalculable ecological damage. In Philip Handler's opinion, only the first of these apprehensions is amenable to scientific evaluation; the latter concerns involve issues of basic social values that merit public discussion but are not yet capable of being resolved.

Public controversy and scientific assessments of the risks of recombinant DNA research have therefore focused primarily on its effects on public health and the environment. Researchers have studied the scientific literature and conducted new experiments to determine whether there is any evidence lending credence to speculations about new pathogenic forms of life. In the meantime, the NIH guidelines are intended to insure use of appropriate biological and physical containment methods. In cases where the presumption of risk is strong and cannot be offset by an important benefit, the experiments have been prohibited until more data are available.

Most speculations of risk cite the lack of knowledge about possible changes in function of the recombined DNA molecule. It is suggested that the joining of a foreign gene with other genes of an organism or vector or the characteristics of the new gene itself might produce some unexpected adverse activity in the new cell environment. If so, the escape of the organism or the accidental transfer of the recombinant DNA molecule to another organism might cause disease in the laboratory worker or human beings, animals, or plants in the surrounding environment.

EXPERIMENTS WITH "E. COLI" K–12 AS THE HOST ORGANISM

The principal host cell employed in current DNA recombinant research is the K–12 strain of *E. coli.* Apprehensions about the use of K–12 arise in part from the fact that other taxonomically related strains of *E. coli* inhabit the human intestine. Several of these "wild" strains may, under certain circumstances, cause disease. Furthermore, because of the dissemination of human intestinal waste products in the environment, it has been suggested that widespread release of *E. coli* K–12 containing a recombinant molecule could have serious adverse effects if interactions occurred with the *E. coli* strains normally present in the human gut or with other organisms in the environment.

Frank Young of the University of Rochester pointed out in his testimony to the subcommittee that all strains of *E. coli* are not alike. He has identified more than 580 biotypes of *E. coli* exhibiting a wide spectrum of pathogenicity ranging from nonpathogenic forms to strains which produce various toxins. Young emphasized that it is necessary to examine the K–12 strain in detail in order to determine whether it poses any hazard.

Philip Handler listed the several questions about K–12 that the special panel of the National Research Council addressed in its November 1977 report. Could the use of this host cell lead to epidemics through some modifications produced by introducing new genomic material by DNA recombinant techniques? Could the recombinant DNA molecule transferred experimentally to the K–12 cell be transferred

in turn to another strain of *E. coli* or other organism if the K–12 cell were accidentially introduced into the intestinal tract? Could some DNA recombinant manipulation produce novel *E. coli* cells which would be pathogenic or ecologically disruptive? Could genes from higher organisms be transferred to any of the prokaryotic cells (cells without a typical nucleus, such as *E. coli* or other bacteria or algae) and be expressed in such a way as to cause harm? Is it possible to construct a host cell for recombinant DNA research which would be so fastidious in its growth requirements that it could not grow outside the laboratory?

Creation of a novel pathogenic E. coli

The Academy panel's conclusions, while not absolute, indicate a negligible risk of creating a novel pathogenic *E. coli* in experiments with the K–12 strain host cell and special variants developed specifically for recombinant DNA work. The K–12 strain lacks the genetic capability to synthesize an important substance involved in the pathogenicity of other strains of *E. coli*. The K–12 strain cannot establish itself as a resident organism in the human intestine and does not multiply in that environment. K–12 is therefore a "safe" research host cell without any modification to reduce further its survival capabilities.

The panel based these judgments in part on the conclusions of a meeting of microbiologists and epidemiologists at Falmouth, Mass., in June 1977.[1] The conference reviewed a variety of experimental findings including the following:

E. coli K–12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts.

Deliberate attempts to induce virulence in K–12 by inserting genes known to regulate virulence factors in other wild strains of *E. coli* failed to produce a fully pathogenic strain of K–12. These experiments used standard genetic methods rather than DNA recombinant techniques.

K–12 deliberately fed to human volunteers soon disappears from the human intestine; in one case limited colonization occurred but did not persist beyond 6 days. The human body defense mechanisms are very effective against K–12; the strain is easily destroyed by normal chemical activities in the intestine.

A deliberate attempt to produce a hybrid of K–12 and *Shigella flexneri*, an organism which can produce infection in the bowel, resulted in a hybrid that picked up genes from *Shigella* but failed to produce any disease and quickly disappeared from the intestines of volunteers who ingested it.

The special nontransmissible plasmids used in recombinant DNA work with K–12 cannot be spread to other host bacteria within the human intestine.

An attempt to produce a virulent K–12 by transfer of plasmids from naturally occurring *E. coli* strains was unsuccessful.

Taken together, these results suggest that K–12 cannot be made pathogenic by processes which convert other varieties of *E. coli*.

[1] The proceedings of the Falmouth conference are published in the *Journal of Infectious Diseases*, vol. 137, May 1978, pp. 613–714.

Transfer of recombinant DNA from E. coli *K–12 to other organisms*

A few scientists argue that while K–12 itself is unlikely to be harmful, its interaction with other *E. coli* strains could produce hazards. Jonathan King of the Massachusetts Institute of Technology observed in his testimony that hospitals have been experiencing increasing numbers of infections from *E. coli* strains other than K–12. This increase is attributed in large part to the acquisition of antibiotic resistant plasmids by *E. coli* bacteria in the intestine. King infers that the escape of a laboratory clone or contact between K–12 and other organisms in the environment could result in the transfer of recombinant DNA molecules to a wild strain of *E. coli* and might induce a new form of pathogenicity. He argued that the evidence summarized in the Academy report and examined at the Falmouth conference is insufficient to conclude that use of K–12 eliminates *any* potential danger from recombinant molecule exchange.

King and other investigators who disagreed with the majority opinion at the Falmouth conference point to the evidence that K–12 can persist in the human intestine for as long as 6 days. In further experiments with variants of K–12 enfeebled by a technique affecting plasmid transferability, transfer did not occur in the intestine but was accomplished in the laboratory; but these researchers suggest that while the probability of transfer of recombinant DNA plasmids from K–12 is low, it cannot be disregarded. Moreover, they claim that insufficient work has been done to insure that transfer by mechanisms other than direct transformation would not occur; nor have any experiments adequately addressed the possibility of gene transfer outside the intestine, in sewer systems, soil or via intermediate hosts.

As yet there is no evidence that transmission of recombinant DNA molecules would be harmful, but researchers are nonetheless attempting to determine the likelihood of such transfers. Oliver Smithies of the University of Wisconsin referred in his testimony to a then unpublished paper[2] reporting that in a 2-year period of monitoring the feces of laboratory workers engaged in nonrecombinant DNA research, no K–12 bacteria or K–12 plasmids with multiple drug resistance markers were ever found. The workers in question were using plasmids capable of being transferred, whereas in recombinant DNA experiments transmission-deficient plasmids are used with a weakened variant of K–12. Thus, the paper concluded that if transmission-proficient plasmids used without any special physical precautions did not appear, there is little if any risk of gene transfer from K–12 plasmids in recombinant DNA work. This study is widely regarded as a significant demonstration of the safety of the K–12 host.

Development of further weakened E. coli *hosts and vectors*

Even though the available evidence shows "normal" K–12 to be a very defective organism, even more enfeebled variants have been developed to prevent colonization and transfer of recombinant DNA in the event of accidental release of the organism. Roy Curtiss of the University of Alabama described his success in producing additional mutational changes in K–12 which greatly limit the ability of the

[2] V. Petrocheilous and M. H. Richmond, "Absence of Plasmid of *E. coli* K–12 Infection Among Laboratory Personnel Engaged in R-Plasmid Research," *Gene*, Vol. 2, No. 5–6, December 1977, pp. 323–327.

bacteria to grow in a nonlaboratory environment. The resulting mutant, named Chi 1776, met the criteria for EK2 containment developed by the NIH Recombinant Advisory Committee and was approved for experimental use by the Director.

Oliver Smithies, a member of the recent Academy panel, discounted any possibility of risk with the host organism constructed by Curtiss and his colleagues. Smithies said in his testimony:

> * * * the negligible risk of Chi 1776 * * * surviving in the feces or of the recombinant DNA plasmid being transferred to some other bacteria becomes less than one chance per 100,000 laboratory workers working for 10,000 years without special physical precautions. (With the application of) physical precautions, * * * the risk is no longer worth considering.

Several essentially nontransferable plasmids have also been developed for use as vectors with K–12 Chi 1776.

Curtiss and others therefore disagree with the suggestion that preference be given or experimentation restricted to use of host cells that do not normally inhabit human beings. Not only are the genetic characteristics of *E. coli* K–12 well known but also substantial evidence of its safety is beginning to accumulate. A requirement to use another host organism would impede research and raise greater uncertainties about potential risks.

USE OF OTHER HOST-VECTOR SYSTEMS

The data on mutant strains of K–12 do not support a conclusion that all recombinant DNA research is without risk. Curtiss argued in his testimony that his own findings should not be applied to any other host-vector system; even knowledge about other variants of K–12 is insufficient. He referred specifically to two host cells of potential interest, *Bacillus subtilis* 168 and *Pseudomonas putida* PpGi. Unlike *E. coli*, both of these bacteria are soil microbes and are nonpathogenic; however, there are few if any data on the factors that influence their survival in a natural environment or their ability to transmit recombinant DNA to other micro-organisms, let alone data on what is required to cripple these organisms in order to prevent their proliferation. Curtiss believes that such data should be collected on alternative host-vector systems before they are approved for recombinant experimentation. Stuart Newman of the State University of New York at Albany in a letter to the subcommittee suggested that once a new host is certified, investigators should closely monitor their experimental cultures to insure that contamination, type reversions, or other unexpected changes have not occurred.

At present, comparatively little effort is being devoted to non-K–12 systems with the exception of *Bacillus subtilus* and a few viral vectors. Yet many researchers with commercial applications in mind believe that *E. coli* K–12 may not be the ideal organism to receive certain kinds of genes and recommend development of a variety of host-vector systems. Ronald Cape took this position in his testimony to the subcommittee. Even in basic research, the failure of gene expression by a recombinant DNA molecule may be a function of the particular host cell environment; and the availability of other host cells would facilitate investigation of a greater variety of DNA functions. For these

reasons, the number of a host of organisms employed in DNA recombinant research and development is very likely to increase.

OTHER CONCERNS

The volume of recombinant material produced will also increase if commercial applications of the technique become feasible. The experience of the biomedical and chemical industries suggests that large-scale production of recombinant organisms will be required in order to obtain useful products in sufficient quantity for marketing. Some researchers insist that special procedures and facilities could prevent escape of these organisms from an industrial laboratory, but the NIH Recombinant Advisory Committee has assumed that probability of escape from containment barriers ordinarily increases with scale. The committee recommended and NIH included in its guidelines a production limit on recombinants known to make harmful products of 10 liters, which is generally adequate for experimental work.

The limit is arbitrary, however, for there are no calculations of the correlation between the volume of organisms and the probability that some of these organisms will enter the environment. Investigations of potential risks associated with recombinant DNA have yet to address this question.

The deliberate release of a recombinant molecule, which is contemplated for various future applications of the technology, is also cause for concern. Although available data indicate that the accidental escape of K–12 would pose minimal risks to health or the environment, its behavior in a variety of natural circumstances has not been examined. For example, no one knows the effects of introducing K–12 containing a recombinant molecule into an environment where sewage treatment is inadequate or where contact with large numbers of different species of bacteria is inevitable. Moreover, alternative host-vector systems are yet to be evaluated. Apprehensions about damage to complex ecosystems are reasonable, particularly if host cells common in the soil or water are used. For the time being, therefore, the NIH guidelines prohibit the deliberate release of recombinant DNA material.

The long-range evolutionary effects of recombinant DNA work are thus ill defined and partly philosophical. Recently published research by Chang and Cohen at Stanford suggests that many of the DNA exchanges previously considered to be unique to laboratory experiments are duplications of natural capabilities of *E. coli*;[3] but these data are limited and do not satisfy all participants in the debate. Robert Sinsheimer of the University of California at Santa Cruz has frequently expressed concern about disrupting the dynamic equilibria among competing species of organisms. In a statement submitted to the subcommittee he concluded:

> The possibilities of long-range environmental hazards, of short- or long-term effects upon basic microbiological equilibria, which are essential to many ecological concerns, remain unaffected by the new observations.

[3] Chang, Shing and Stanley N. Cohen, "In Vivo Site-Specific Genetic Recombination Promoted by the EcoRI Restriction Endonuclease," *Proceedings of the National Academy of Sciences*, vol. 74, No. 11, November 1977, pp. 4811–4815.

Current Federal Regulation of Research

ORIGIN AND PROVISIONS OF THE NIH GUIDELINES

Research with recombinant DNA molecules has been subject to voluntary or involuntary restrictions almost from its inception approximately 5 years ago. Participants in the 1973 Gordon Conference on Nucleic Acids raised the possibility that some experiments could be hazardous and urged the National Academy of Sciences to create a study group to recommend guidelines or other appropriate action. The following year the NAS committee proposed that scientists voluntarily "defer" certain experiments that might, indirectly, encourage the spread of antibiotic resistance, toxin formation, and cancer-causing or other animal viruses. Other recommendations of the committee led to the creation of the NIH Recombinant DNA Molecule Program Advisory Committee in 1974 and to an international meeting of scientists and others at Asilomar, Calif., in February 1975.

The consensus at Asilomar was that most of the contemplated work with recombinant DNA should proceed but that precautionary measures should be used to minimize the spread of artificial recombinant DNA's in human populations or other nonlaboratory environments. From the publication of the Asilomar report in May 1975 until June 1976, the conference recommendations guided NIH-supported investigators and, apparently, were observed by scientists throughout the world. In the meantime, the NIH Recombinant Advisory Committee proceeded to draft a more detailed set of guidelines to govern NIH research projects. The Director of NIH issued these standards on June 23, 1976, and they were published in the Federal Register of July 7.

The National Science Foundation, Department of Agriculture, and other Federal agencies subsequently agreed to apply them to their own grantees or in-house research activities. Other nations followed suit. British guidelines were announced in August 1976 and Canadian guidelines early the following year. More recently, guidelines have also been published in France, the Federal Republic of Germany, and the Soviet Union and are in preparation in other countries. According to a report on a recent survey by a Federal interagency committee, some 175 research projects are being conducted in Europe, Canada, Australia, Japan, and the Soviet Union under various safety procedures, most of them modeled on the NIH or United Kingdom guidelines.

The NIH guidelines take several complementary approaches to preventing the spread of possibly harmful products of recombinant DNA research. First, certain experiments continue to be prohibited. Examples are the introduction of antibiotic resistance traits to pathogenic organisms and the formation of recombinant molecules containing genes for the production of dangerous toxins. Second, deliberate release into the environment of any organisms containing recombinant DNA is forbidden. Third, experiments producing more than 10 liters of culture containing recombinant DNA known to make harmful products are also banned. Fourth, permitted experiments must be conducted with procedures and equipment intended to prevent the escape of recombinant DNA material into the immediate or general

environment. These measures of "physical containment" are grouped into four categories, P1, P2, P3, and P4, each level more stringent than the one preceding to correspond to the presumed potential risks of various experiments. Fifth, researchers must use biologically weakened vectors and host organisms that are unlikely to survive in a nonlaboratory environment or exchange DNA with other organisms. These materials are also graded, EK1, EK2, and EK3, to provide "biological containment" commensurate with the potential risk of harm. Before they can be used in recombinant experiments, EK2 and EK3 host-vector systems must undergo extensive testing, review by the Recombinant Advisory Committee, and certification by the Director of NIH.Thus, permitted experiments are assigned levels of physical and biological containment which are to a degree interchangeable; an increase in biological containment may permit a lowering of physical containment requirements.

EFFECTS OF THE GUIDELINES

According to testimony before the subcommittee, these measures, taken together, provide a high degree of protection of public health and the environment. Philip Handler stated the conclusion of the National Academy Panel on Risks and Benefits of Recombinant DNA Research, whose members included authorities in molecular biology, genetics, infectious diseases, and epidemiology. He quoted:

> Currently available evidence leads us to conclude that the many benefits of recombinant DNA research and technology can be achieved with negligble risks to the biosphere when the work is carried out within the NIH guidelines.

Despite minor reservations about the permissiveness of the standards, Bruce Levin of the University of Massachusetts characterized their approach to the unknown risks of recombinant DNA as properly one of "extreme prudence." Paul Berg, Frank Young, Roy Curtiss and others generally agreed with this assessment.

In the past, physical containment procedures similar to those required by the NIH guidelines appear to have been effective in preventing infections from human pathogens used in research. In other public testimony, the Director of the National Cancer Institute's Office of Research Safety described the experience with high containment at the former biological warfare laboratory at Fort Detrick, Md. During a 10-year period ending in December 1969, only one laboratory-acquired infection occurred as a result of an accidental glove puncture. The environmental impact statement accompanying the guidelines included an analysis of laboratory-acquired infections data from the Center for Disease Control, the National Animal Disease Center, and the National Institutes of Health as well as Fort Detrick; it found no case where a disease was transmitted from an infected laboratory worker to another person. The EIS noted that only eight such cases have been documented for other American and foreign laboratories. In short, scientific research with pathogens under stringent containment appears to have an excellent safety record.

Roy Curtiss and others who have attempted to calculate the risks of survival and reproduction of a weakened test organism or vector should physical containment fail believe that these risks are exceed-

ingly small. Although the probability of survival is greater at lower levels of biological containment, the experiments permitted at these levels generally involve organisms known to exchange genetic information by natural processes.

On the other hand, neither the containment measures nor the assessments of their effectiveness are infallible. In the opinion of Jonathan King, even a small number of accidents might do irreparable harm if a deleterious combination of genes should establish itself in the environment. He believes that monitoring of laboratory workers' health and maintenance of medical records have been inadequate. In the absence of base-line health data, it is not possible to judge the effectiveness of physical containment methods which are, in any event, entirely dependent upon the training and behavior of laboratory personnel. Others have pointed out that the conduct of research with known pathogens may be quite different from the conduct of experiments for which no hazards have been demonstrated. Arthur Schwartz, a University of Michigan mathematician, questioned the calculations of potential risks in recombinant DNA research. He stated in his testimony to the subcommittee that in his estimation the methods used by Curtiss and others to estimate probabilities are flawed because they do not take account of multiple factors and successive events.

The majority of scientists, however, considers the present rules too stringent, particularly with regard to the use of K–12 bacterial hosts and plasmid vectors. Curtiss and others urged approval of the revisions of the guidelines recommended in September 1977 by the Recombinant Advisory Committee; these changes would generally reduce the physical and biological containment requirements for *E. coli* experiments. Nevertheless, Paul Berg observed that most scientists accept the present guidelines as "an interim solution to the anxieties that remain." No testimony at the subcommittee hearings suggested that the rules per se have greatly impeded progress in recombinant DNA research, although they have added to its cost and inconvenience and undoubtedly entailed some delays. Referring to the more than 300 NIH-funded research projects and the recent accomplishments in cloning the rat insulin gene and producing somatostatin, Marshall Shapo of the University of Virginia concluded that "research has indeed flowered. * * * That seems to me * * * to indicate that regulation and talk of regulation has not been either chilling or productive of inefficiency, given the uncertainty that originally existed."

That most researchers have accommodated themselves to regulation and that regulation has permitted dramatic advances in research do not justify the continuation of unnecessary restrictions. The subcommittee inquired whether the current work in risk assessment is likely to remove all reasonable doubt about the safety of recombinant DNA experiments and thus the need for regulation. The responses suggest that most scientists expect further research to justify a selective relaxation of the containment standards, but they view this as a gradual process. They do not reject the possibility of discovering some hazards. Roy Curtiss predicted that within 2 or 3 years scientists will have acquired "adequate information" on *E. coli* K–12 but cautioned that it will take longer to evaluate new host systems.

Jonathan King rejected the notion of a short-term risk assessment program. He said, "Evolution goes on; new niches occur in the environ-

ment, and the research proliferates. New and more ingenious kinds of experiments are proposed." And Paul Berg agreed that a 2-year evaluation is not sufficient. In view of the likelihood that considerable uncertainty will remain, particularly about newly developed techniques and host-vector systems, there is broad support for continuing to prohibit certain recombinant DNA experiments and control others, provided that there is opportunity to relax or remove restictions on research that is shown to pose no significant risk. Marshall Shapo suggested, "* * * Where present foresight of some possible risks remains dim, regulation is justified to a level that corresponds with the uncertainty, though not a more stringent one."

DEFICIENCIES OF THE GUIDELINES

Coverage

Although Federal sponsors of research with recombinant DNA other than NIH have adopted its guidelines, there appears to be great variation among their respective review procedures; initial evidence suggests a very superficial approach by some Federal agencies. The subcommittee is inquiring further about the activities of the National Science Foundation, the Department of Agriculture, the Veterans' Administration, and the Department of Energy, and will report its findings at a later date. Thus far the principal concern of Government officials, public interest groups, private industry, and State and local officials has been that privately supported research activities in universities and industry are not subject to the NIH standards or external review except on a voluntary basis.

In issuing the 1976 regulations, Donald Fredrickson, Director of NIH, urged all Government agencies and "all who support or conduct such research throughout the United States" to adhere to the guidelines voluntarily. In November 1976, the Environmental Defense Fund and the Natural Resources Defense Council petitioned the Secretary of HEW to promulgate regulations governing all recombinant DNA activities in the United States under the authority granted by section 361—Control of Communicable Diseases—of the Public Health Service Act (42 U.S.C. 264). Members of the Pharmaceutical Manufacturers Association and other industrial firms which have agreed to observe the guidelines urge that their coverage be formalized.

The concern is not merely about compliance by unregulated sponsors and performers of research. As the president of the PMA and the president of Cetus Corp. observed to the subcommittee, the present guidelines are written for Federal grantees. Commercial firms have had ample opportunity to comment on the standards and the proposed revisions, and have consulted NIH officials on their interpretation, but they have no representation on the Recombinant Advisory Committee nor on the Advisory Committee to the Director of NIH which reviews changes in the guidelines. Private laboratories may be prevented from receiving recombinant DNA materials from an NIH grantee for lack of certification or may be handicapped in their research and development efforts by the 10-liter limit. At present, there is no formal mechanism for resolving issues that concern the private sector. As more private firms enter recombinant DNA research and as the research becomes more sophisticated, the private sector is likely to experience

greater difficulty in complying with the guidelines. Ronald Cape of Cetus Corp. stated, "We want to be treated both in the letter as well as the spirit like everybody else in terms of these guidelines."

Procedures

The effectiveness of the NIH guidelines does not depend upon reasonable standards alone. It also requires procedures to review and enforce compliance. It cannot be argued that the guidelines are merely advisory. The October 1977 environmental impact statement on the 1976 guidelines states that "Noncompliance with the guidelines will result in termination of funding of research grants and contracts." Yet NIH's lack of experience in regulation is indicated by the ambiguity of the guidelines' procedural provisions, by the guidelines' failure to establish clearly the responsibilities of institutions, institutional biohazards committees and investigators, and by the absence of any mention of procedures to investigate and correct violations. While undoubtedly most researchers have observed the guidelines conscientiously, it is equally clear that others have substituted their own judgments of safety for those of NIH.

These conclusions result from the subcommittee's investigation of an acknowledged violation last year by researchers at the University of California at San Francisco Medical School, reported originally in the September 30, 1977, issue of Science magazine. The case involved the unauthorized use of an EK2 plasmid vector with *E. coli* χ 1776 in a P3 experiment to clone the rat insulin gene. The vector in question, pBR322, was submitted to NIH for certification in December 1976, approximately 6 months after publication of the guidelines in the Federal Register. The experiment using pBR322 was conducted from mid-January to mid-March, 1977, at which time the organisms containing the recombinant DNA were destroyed. Subsequently, the experiment was successfully repeated with an authorized vector. The plasmid pBR322 was not certified by NIH until July 7, 1977.

Chapter IV of the guidelines—"Permissible Experiments: *E. coli* K–12 Host-Vector Systems" states, "For the time being, no EK2 or EK3 host-vector system will be considered bona fide until the Recombinant Advisory Committee has certified it." This requirement is intended to insure that material used in moderate- and high-risk experiments has a very low probability of surviving and exchanging DNA with other organisms in a natural environment. In fact, the language of the section is misleading; it is the Director of NIH who certifies EK2 and EK3 vectors after review and upon recommendation by the Recombinant Advisory Committee (RAC). Nevertheless, a November 26, 1976, NIH memorandum advised all institutional biohazards committees that only one EK2 host-vector system had been certified, and that when others were certified, "You will be notified and their availability will be announced in the 'Nucleic Acid Recombinant Scientific Memoranda.' " The memorandum also states that the institutional biohazard committees are responsible for informing researchers at their institutions of NIH policies and actions. In any event, on January 16, 1977, the Recombinant Advisory Committee only tentatively recommended approval of pBR322 subject to the receipt of additional data supporting its safety; these were submitted in early February. Further experimental data were requested by the committee

in late March in accord with newly adopted test criteria for EK2 vectors. The committee finally recommended certification of pBR322 on June 23.

In his testimony to the subcommittee, William Rutter, chairman of the UCSF Department of Biochemistry and Biophysics and a member of the insulin research team, attributed the premature use of pBR322 to information that the RAC had fully "approved" the vector in January and to a literal interpretation of the guidelines' reference to certification by the RAC. He also argued that he and his colleagues were convinced of the vector's safety by the supporting data given to NIH: "By one criterion of 'safety,' this plasmid is 10,000 to 1 million times better than EK2 plasmid vectors then approved." Herbert Boyer, a member of the UCSF department who developed pBR322 and applied for its certification, testified that he was aware that it had not been certified in January but did not immediately inform members of the insulin team and did not discover that they were using it until early March. Director Fredrickson agreed that there had been understandable confusion about NIH procedures in early 1977 but stated that NIH had subsequently improved its communications with grantees. Boyer and Rutter assured the subcommittee that the university had also adopted new procedures to prevent similar occurrences.

Although the use of pBR322 posed no hazard to the researchers or others, the subcommittee believes that the incident has serious implications for Government and institutional regulation of recombinant DNA research. Documents and testimony in the record of the subcommittee's hearing support the following additional findings concerning this violation:

> Contrary to the implication of its November 1976 memo, NIH did not promptly notify applicants or prospective users of host-vector systems in writing of the actions by the RAC or the Director. Researchers at UCSF who decided to proceed with the pBR322 experiments relied on information from technicians in their laboratory who said they had heard, indirectly, that the vector had been approved. No one on the research team attempted to confirm its status with NIH officials or consulted the biohazards committee prior to the experiments.
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> Approximately 3 weeks after the experiments commenced. Boyer scheduled a meeting at which he informed members of the insulin team that pBR322 had not been certified; apparently, they did not reveal that they were using it. The researchers continued to grow and examine the host organisms in which they had inserted the plasmid in order to determine whether they contained the recombinant DNA.
>
> At the meeting in early February, Boyer also announced that a log book would be kept to record use of the P3 laboratory. (Neither the guidelines nor the institutional biohazards committee required such a log book.) No official entries were made, however, until mid-March. At that time the use of pCR1, the first certified vector, was recorded retroactively to February 1. Later, the use of pMB9, certified in April, was also listed. There was no reference, however, to the use of pBR322 in the interim.

In the absence during this period of the principal investigator on the insulin project, Howard Goodman, Boyer was designated to NIH as the acting principal investigator. Goodman also asked Brian McCarthy, another member of the department, to be available to advise the investigators in his laboratory. Boyer and McCarthy also shared responsibility for supervising the newly constructed P3 facility. Both knew that pBR322 had not been certified but claim they were unaware of its use by two postdoctoral fellows conducting the experiment, Axel Ullrich and Jonathan Shine.

Shortly after the first of March, Goodman and Rutter discovered that pBR322 had not been certified. They attempted to ascertain from NIH whether certification was imminent. Finding that there would be a further delay, Rutter called the NIH Deputy Director for Science, Dewitt Stettin, between March 16 and March 19 to seek his advice about the continuing use of the vector. Rutter was advised to destroy the host organisms; at that point he and Goodman decided to terminate the experiment. The Deputy Director did not inform the NIH Office of Recombinant DNA Activities (ORDA) or other officials of the call.

In late May a member of the Rutter laboratory staff informed David Martin, chairman of the UCSF biohazards committee, of the pBR322 incident. After making a personal inquiry, Martin told a meeting of the committee on June 3 that researchers had used a vector on the advice of NIH officials who predicted its "imminent" certification. When certification was not forthcoming, the researchers had to destroy their work "to avoid noncompliance with the director's wishes, although consistent with the guidelines." The committee approved a letter of complaint to NIH that referred to the delay in certifying pBR322 but not to its use. It was not until September that the full committee learned of the violation.

Apart from Rutter's call to the Deputy Director in March, no one at UCSF reported the incident to NIH; officials of ORDA and the Office of the Director did not learn about it until late summer when the Science reporter inquired. Even then, no investigation was made; rather, ORDA requested a written report from the new chairman of the biohazards committee, James Cleaver, for the purpose of answering further public inquiries to NIH. Although the report, dated October 25, indicated that the experiment continued for several weeks after the investigators discovered that the vector was not certified and that neither the biosafety committee nor NIH was fully apprised of the incident, NIH took no further action until prompted by the subcommittee's investigation. On December 1, ORDA asked for a supplementary written report from the biohazards committee chairman.

The UCSF violation occurred shortly after NIH issued procedural instructions for implementing the guidelines and coincided with the formulation of test criteria for host-vector systems. It resulted in part from confusion about the NIH approval process. Witnesses stated that NIH has since improved its publication of certification actions and clarified the roles of the RAC and the Director. Accord-

ing to William Rutter, the system is now tighter and more business-like. Be that as it may, the researchers who conducted the experiments neglected to confirm the rumor of pBR322 approval and then delayed correcting their error in the hope that the obvious remedy would not be necessary. The acting principal investigator, the biohazards committee, and other permanent members of the department exercised so little supervision that they did not discover the use of the uncertified vector by their colleagues. Director Fredrickson left the subcommittee with no doubt that this lack of action was contrary to the intent of the NIH guidelines.

The guidelines themselves, however, are deficient. They require grantees to report accidental equipment failures and problems of operation and implementation of safety procedures but make no provision for reporting or investigating violations. Only an unusual set of circumstances, not monitoring by the institutional biohazards committee or NIH, brought the incident to light after the researchers had decided to keep it to themselves. It is not at all clear, as Fredrickson maintained, that the institutional committee is the proper body to investigate allegations of a violation. In the absence of any standard procedure, both the local committee and the Office of Recombinant DNA activities failed to conduct a thorough inquiry and relied instead on statements by the principals. Finally, the episode demonstrates the inadequacy of the guidelines' enforcement mechanisms; NIH has little recourse other than to withdraw the grant of the principal investigator, who seemingly bears less responsibility in this matter than other members of the department and the biohazards committee.

Appropriate legislation and reasonable regulations can formally correct these deficiencies but will not have universal acceptance. Not the least disturbing testimony in the affair was William Rutter's rationale for secrecy—the researchers' presumption of safety and fear of exacerbating public controversy. First, he said, "the Recombinant DNA Committee had voted to approve the plasmid as an EK2 vector. The DNA insert was placed in a region of the plasmid such that it was unlikely it could be read or expressed. The experiment had been carried out with no ill effect." Second, an "inflamed social and political climate * * * existed with respect to recombinant DNA technology. * * * The press, among others, had sometimes fanned the flames of controversy. * * * Repressive and punitive legislation was being considered." This assumption of superior judgment threatens not only regulation but also productive scientific inquiry. If even a few scientists ignore the common ground rules of research, they undermine the basis of healthy scientific competition. If they are discovered, they undermine public confidence in their enterprise. It is clearly in the interest of the scientific community to cultivate a willingness to comply with the guidelines. No enforcement system can ever fully substitute for a spirit of good faith observance among investigators.

Regulation of commercial applications

As previously mentioned, the subcommittee heard several predictions that practical commercial applications of recombinant DNA technology will be feasible within a few years, much earlier than

was previously assumed. The success of the California investigators in cloning the rat insulin gene and in developing a synthetic gene for the production of the hormone somatostatin points to the possibility of producing a variety of hormones and industrial enzymes in large cultures of recombinant DNA organisms. Presumably, the organisms would be contained and eventually destroyed, as they are in the research laboratory; but their large volume would increase the likelihood of worker exposure and escape of the organisms from the facility.

More speculative uses actually contemplate the deliberate release of the modified host cell into the environment for some specific purpose such as the conversion of organic material in sewage treatment, the oxidation of petroleum spills, or improvement in the nitrogen-fixing capability of plants. Aside from the possible hazards of the organism itself, these uses may have adverse indirect effects. Plants with superior nitrogen-fixing characteristics might displace others or valuable resources be destroyed. Alternatively, there has been mention of using a modified vector, probably a virus, to infect plants or destroy insect pests. In these cases, environmental exposure, for example, from spraying, would be difficult to control. The use of a modified vector for correcting a genetic defect in man raises moral as well as safety concerns.

The NIH guidelines do not purport to deal with these possibilities and the apprehensions they raise. Indeed, if they were applied to the private sector, the 10-liter production limit on certain cultures, the ban on release, and the physical containment measures might singly or in combination preclude all of these applications. More importantly, uses involving the introduction of recombinant DNA molecules into a natural environment run directly counter to the concept of biological containment which is a principal safeguard in the guidelines. The utility of the modified organisms or vectors would depend entirely upon their ability to survive and/or exchange DNA with other organisms, whereas the hosts and vectors now prescribed for research are specifically designed to have no such capability.

It is impossible to predict what will be the perception of recombinant DNA hazards and the status of the guidelines when and if any of these applications becomes feasible. For the present, the risks in commercial exploitation of the technology appear to many observers to be more varied and more serious than any that may be associated with research experiments. Roy Curtiss doubted that commercial uses of genetically modified micro-organisms would pose "any threat to the public or the well-being of any other organisms in the environment," but said, "I think it is essential in these applications of recombinant technology that we obtain appropriate experimental evidence to validate this general belief." David Newburger of Washington University, St. Louis, Law School expressed concern that the issue had not been addressed in previous discussions of recombinant DNA regulation.

PART II—RECOMMENDATIONS

Recommendations for Regulation of Research

LEGISLATIVE AUTHORITY

In response to the concern that some recombinant DNA research was unregulated, the Secretary of HEW convened an interagency committee in the fall of 1976 under the chairmanship of Director Fredrickson. The committee included representatives of the Federal agencies and departments sponsoring and conducting recombinant DNA research and those having regulatory authority that might be applicable in this area. Its first task was to consider whether the extension of the guidelines beyond NIH to the public and private sectors could be accomplished under existing statutory authority or whether new legislation was required. Having reviewed the relevant statutes, the Interagency Committee reported in March 1977 its conclusion that "no single legal authority or combination of authorities currently exists that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements." Dr. Gilbert Omenn, Assistant Director of the Office of Science and Technology Policy, reiterated this position in his testimony to the subcommittee on November 8; and it was generally supported by Marcia Cleveland, attorney for the Natural Resources Defense Council, in a December memorandum requested by the chairman of the subcommittee.

The Interagency Committee rejected use of the Occupational Safety and Health Act of 1970, the Toxic Substances Control Act, the Hazardous Materials Transportation Act, the authorities of the Food and Drug Administration and the Center for Disease Control and several more specialized statutes primarily on the grounds that they could not be extended to cover all performers or all aspects of research with recombinant DNA. For example, the Occupational Safety and Health Act defines "employer" to exclude States and their political subdivisions unless the OSHA standards are voluntarily adopted. Twenty-six States have not done so and thus their public universities would not be subject to Federal regulation. Section 5 of the Toxic Substances Act exempts from the requirement of registration with EPA those chemical substances used in small quantities for the purpose of scientific experimentation or analysis. The Hazardous Materials Transportation Act would not apply to the handling of recombinant DNA materials in the laboratory. The licensing authority of the Center for Disease Control under section 353 of the Public Health Service Act is limited to clinical laboratories. FDA's authorities are generally interpreted to reach the manufacture only of commercial products.

The Interagency Committee found no such obvious deficiencies in section 361 of the Public Health Service Act, on which the Environ-

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mental Defense Fund relied in its petition to the Secretary of HEW. This section authorizes the Surgeon General, with the approval of the Secretary, to "make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases" from foreign countries into the United States or from one State to another. He may provide for "inspection, fumigation, disinfection, sanitation * * * and other measures" to carry out such regulations.

Section 368 provides for a fine of $1,000 or imprisonment for not more than 1 year, or both, of persons who violate the regulations under section 361. The Interagency Committee suggested that this authority could be broadly interpreted to support regulation of most recombinant DNA research activities, although it might not apply to research with materials that could pose a hazard only to nonhuman animals, plants, or the environment. On the other hand, unless a reasonable basis could be shown for concluding that the products of recombinant DNA research might actually cause human disease and be communicable, the Interagency Committee was concerned that the regulations might not withstand legal challenge.

Although the Carter administration endorsed the Interagency Committee report and proposed legislation that was introduced in the last session in both Houses, the failure of Congress to act in the following months led the executive to reconsider alternative ways of insuring universal compliance with the NIH research guidelines. In his testimony to the subcommittee on November 8, 1977, Office of Science and Technology Policy Director Frank Press proposed that the Department of Commerce undertake a program of "voluntary compliance and meaningful surveillance" involving businesses engaged in recombinant DNA research. Press said that the Department planned to consult with pharmaceutical and other firms on appropriate procedures for external monitoring of their recombinant DNA research activities. These discussions are still in progress.

Following its hearings, the chairman of the subcommittee wrote to Press and HEW Secretary Califano in part to ask their current views on the use of section 361 to regulate either research with or commercial applications of recombinant DNA. At the same time, OSTP requested HEW to reconsider use of this authority in the absence of new legislation. In his reply to the subcommittee, the Secretary stated, "Our office of the General Counsel * * * believes it is preferable for a regulatory effort of the magnitude required to oversee all recombinant DNA activities, whether or not known to affect human health, to be based on the explicit support of the Congress as well as that of the administration, particularly in light of the active interest the Congress has shown in this area. The consensus needed for this type of program is not best established by applying a general provision of law to this specific situation."

In a separate letter to the subcommittee, Frank Press acknowledged Secretary Califano's preference for specific legislative authority. OSTP had, nevertheless, reviewed the administrative history of section 361 and concluded that its application to recombinant DNA research would be appropriate. Press pointed out that the Public Health Service and the Food and Drug Administration have used the act's unusually broad delegation of authority in a variety of ways to regu-

late drinking water, milk and animal products, shellfish and pet turtles that might pose a danger to public health. Even noninfectious materials have been regulated. These applications, according to Press, show a clear "preference for prevention of the occurrence of any risk, rather than control of the spread of infection." In the absence of conclusive evidence to the contrary, the possibility that recombinant DNA research on nonhuman animal or plant materials could result in human infection would justify comprehensive regulation of the research under this authority. For these reasons, the Office of Science and Technology Policy reserves the option of recommending that regulations be issued under section 361 if legislation is long delayed.

Views of the subcommittee

The subcommittee believes that the Federal Government should rely on full legal authority in regulating all recombinant DNA research regardless of its locale or sources of financial support. A program of voluntary compliance by and monitoring of industrial research activities is insufficient. Whatever form such a program might take, it would leave unclear the status of privately supported research in universities. Moreover, because it would require the consent of all participants, there is no assurance that it would achieve universal coverage in the private sector. It would not afford those subject to it an adequate voice in the drafting or subsequent revision of the guidelines. The lack of effective sanctions for violations would undermine public confidence that the guidelines were being observed. Finally, duplication in the Department of Commerce of expertise which resides in the Department of Health, Education, and Welfare and elsewhere would be wasteful and unnecessary.

The subcommittee agrees that the Occupational Safety and Health Act, the Toxic Substances Control Act, the Food, Drug and Cosmetic Act and other specialized public health and environmental protection statutes do not provide adequate authority to regulate all research with recombinant DNA, although, as Secretary Califano observed in his letter to the subcommittee, the Food and Drug Administration "* * * could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the NIH Guidelines on recombinant DNA," and could inspect firms making such certification. Use of this authority, even though it would apply only after the research had been conducted, would be an important incentive for companies subject to the food and drug laws to comply with the NIH standards. Furthermore, as the Interagency Committee observed OSHA, FDA, and EPA will have important roles to play when recombinant DNA techniques reach the stage of commercial application. (See Applicability of Existing Statutes, p. 41.)

The subcommittee is not persuaded that the legal obstacles to use of section 361 of the Public Health Service Act are insuperable. While it is the case that no person is known to have been injured by exposure to recombinant DNA material, the possibility of unintentionally transferring a pathogenic characteristic capable of causing disease in laboratory workers or others in the surrounding environment is the principal concern that led to the Asilomar conference recommendations, the NIH guidelines, and the similar precautionary

measures adopted in numerous other countries. The further possibility that such a disease would be resistant to present methods of prevention and treatment enhances the reasonableness of these measures.

Section 361 does refer only to communicable diseases affecting human beings. Presumably, there are or will be recombinant DNA experiments that could pose a risk of injury to plants, animals, or the environment but not of human infection. If necessary, however, the protection of nonhuman animals and plants might be achieved in cooperation with the Secretary of Agriculture using his authority under the animal quarantine laws (21 U.S.C. 111, 114, 114(b), 123, and 134(a)) and the Federal Plant Pest Act (7 U.S.C. 150bb and 150dd), which are similar in purpose and structure to section 361. (See letter from the Secretary of Agriculture in appendix.)

In any event, according to recent court opinions, the National Environmental Policy Act (42 U.S.C. 4321 et seq.) imposes a duty on Federal agencies to protect the environment in all major actions whether or not an authorizing statute specifically provides for environmental protection.

Of greater concern to the subcommittee is whether an effective and appropriate regulatory system could be established under section 361. Its use to prohibit certain kinds of scientific experiments, prescribe standards for the conduct of others, certify research facilities, or register research projects would indeed be unprecedented. The act would not limit the power of State and local governments to impose standards at variance with the Federal standards. The criminal penalties in section 361 would be inappropriate except for the most serious willful violations of the regulations that result in harm. Nevertheless, the agency is the appropriate one and the delegation of authority broad. The Secretary or Surgeon General would not be encumbered by specific statutory requirements in revising or rescinding regulations as warranted by new scientific evidence. There is also merit in avoiding the necessity for Congress to legislate, perhaps repeatedly, in highly technical areas of scientific research that are conceivably but not demonstrably hazardous.

The subcommittee has not reached a final judgment on the legal issues relating to the use of section 361 of the Public Health Service Act to regulate recombinant DNA research. In view of the Secretary's apparent desire for specific new authority for this purpose, the subcommittee believes that legislation is the more likely and preferable course of action. However, the subcommittee recommends that the Secretary of HEW give serious consideration to promulgating standards and procedures under the authority of section 361 if Congress does not complete action on legislation or if the legislative committees with jurisdiction conclude that existing authority is adequate. The Secretary should prepare for this contingency. The testimony before the subcommittee left no doubt that the application of NIH standards to all recombinant DNA research should be accomplished as expeditiously as possible.

SCOPE, IMPLEMENTATION AND DURATION OF LEGISLATION

The consensus that regulation of all recombinant DNA research should be "based" on sections II (Containment) and III (Experimen-

tal Guidelines) of the NIH guidelines does not resolve a variety of controversial and technical legislative issues. How should recombinant DNA research activities be defined? Should regulation be temporary in the expectation that further research will demonstrate the safety of all recombinant DNA experimentation or that public concern will diminish? Should legislation simply extend the present NIH standards to non-NIH-funded research projects or require new regulations to be issued? Are the July 1976 guidelines or the changes recommended to the Director of NIH by the Recombinant Advisory Committee the appropriate basis of regulation? What provisions should be made for future changes in the standards to reflect new scientific evidence of greater or reduced risk? Should legislation exempt from the standards experiments that are proven to be safe or to duplicate DNA exchanges that occur naturally?

Several of these questions reflect the concern of the scientific community that needless restrictions may be instituted and thereafter perpetuated. For example, there have been various proposals to appoint a committee of experts to study the evidence relating to the hazards attributed to recombinant DNA research and to report its findings to Congress and the executive branch within a specified time. Proponents of a study commission appear to assume that further scientific investigation will show that most if not all recombinant DNA experiments pose negligible risks to health and the environment. On this assumption that regulation will be necessary only until the commission has completed its work, they favor short-term or "interim" legislation. Various witnesses before the subcommittee supported the inclusion in legislation of a sunset clause that would compel Congress to reconsider the need for regulation of recombinant DNA research after a few years.

The subcommittee also heard proposals to limit the scope of regulation. Philip Handler urged that only P3 and P4 facilities be required to be licensed and inspected. Halvorson would exempt P1-level experiments from all regulation. Others have recommended that the law direct the Secretary to identify "non-novel" experiments, producing DNA recombinants that are known to occur in nature and are therefore presumably safe; these would be exempt from regulation altogether. Alternatively, the definition of recombinant DNA research activities could exclude certain kinds of experiments.

A related issue concerns the pending revisions of the physical and biological containment standards required by the July 1976 guidelines. These changes were recommended by the NIH Recombinant Advisory Committee, published in the Federal Register on September 27, 1977, and are now being considered by the Director. In the subcommittee's hearings, representatives of environmental organizations argued that no conclusive evidence exists to justify relaxation of the present standards. On the other hand, several scientists, while approving some prohibitions and restrictions on experiments, are convinced that these requirements are too stringent, at least with respect to uses of *E. coli* K–12 host-vector systems. They preferred that the proposed revisions of the guidelines be the basis of regulation under new legislation. A number of witnesses urged that any future administrator have authority to modify the standards in light of new scientific data, whether such

evidence reveals that the risks are greater or less than is now thought to be the case.

There have also been various suggestions for incorporating the guidelines in law. The simplest approach is said to be a provision that, upon enactment of legislation, the guidelines will be applicable to all sponsors and conductors of recombinant DNA research without further administrative action. A second alternative, which anticipates the need for procedural provisions appropriate to the private sector, is to extend the guidelines as interim rules and require the promulgation of final regulations within a specific period of time. Third, Congress could dispense with the interim extension of the guidelines and require that comprehensive regulations be issued.

Views of the subcommittee

The subcommittee believes that knowledge of the effects of recombinant DNA experimentation will be acquired over the course of years in the normal process of scientific investigation. Progress in assessing its safety will be accompanied by rapid development of the technique and use of a variety of host-vector systems, each requiring evaluation. From this perspective, the subcommittee prefers the creation of an advisory apparatus, including scientists and lay persons, operating on a continuing basis rather than a special commission directed to reach a final judgment within an arbitrary time period. When the prospective uses of recombinant DNA techniques are better known, it will be necessary to address the moral and public policy issues of human genetic engineering, perhaps by a Government-appointed group of experts and laypersons. Because these advanced applications are not yet subject to verification or regulation, however, the subcommittee believes that legislation should deal only with the health and environmental consequences of recombinant DNA research. On the other hand, it sees merit in a sunset provision to insure a reassessment of both the need for and effectiveness of Federal regulation. Since these judgments cannot be made for some time after the regulations become effective, the subcommittee recommends that the law expire no earlier than 3 years after its enactment.

The legislation's definition of recombinant DNA should be the definition in the current NIH guidelines. The administering agency should have authority to remove restrictions on certain categories of experiments; but the criterion should be that the experiments pose no significant risk to public health or the environment, and the test procedures and criteria for assessing such risks should be published with the regulations. The concept of "non-novelty" is ambiguous and not invariably indicative of safety. The subcommittee recognizes a certain anomaly in restricting operations that occur in nature but believes that the basis for removing such restrictions should be consistent with the purpose of the legislation. To insure that important risk-assessment studies can be carried out, the subcommittee recommends that the administrator be authorized to waive the ban on presumably dangerous research for individual experiments to be conducted under specified conditions and supervision.

The scheduling of the subcommittee's hearings shortly after publication of the proposed revision of the guidelines did not permit a

thorough examination of the recommended changes, but the subcommittee accepts the view that recent findings justify a careful revision of the physical and biological containment standards for certain experiments. There is also a clear need to correct existing procedural deficiencies and to devise ways of applying the standards to privately supported research activities, including appropriate methods of monitoring and enforcing compliance. Because the sanctions and administrative section of the current guidelines are predicated upon the NIH grant review process, legislation cannot merely "extend" the guidelines to the private sector.

For these reasons, the subcommittee favors a provision requiring promulgation of standards and requirements necessary to secure and maintain compliance as soon as practicable after passage of legislation. This approach would permit both substantive and procedural amendments to the guidelines. The subcommittee strongly supports the discretion of the administering agency to make further changes in the standards, provided that the supporting evidence is published and there is ample opportunity for public comment. In order to avoid prolonged delay in issuing the initial regulations, however, it may be necessary to modify the requirements of the Administrative Procedure Act.

WHO SHOULD REGULATE

The recombinant DNA debate has generated a variety of proposals for national and local regulatory agencies, commissions, and committees. At issue is the extent to which research scientists should be entrusted with responsibility for their own conduct, individually or through peer review, or be subjected to external scrutiny and control. Related issues are the proper balance between Federal and State or local responsibilities and the appropriate role of lay persons in the regulation of recombinant DNA research.

In legislative terms, these issues raise the following questions: First, which Federal agency should have authority to issue and enforce rules governing recombinant DNA research? Second, what apparatus should be established to provide expert assessment of the risks associated with such research and to recommend measures to protect public health and the environment against those risks? Third, what should be the responsibilities of institutions and investigators conducting recombinant DNA research? Fourth, should the Federal Government preempt the authority of States and localities in the interest of uniform regulation?

Federal agency

Several witnesses discussed the merits and drawbacks of leaving regulatory authority with the National Institutes of Health. Joseph Grady of the Upjohn Co.'s Department of Infectious Disease Research and William Rutter of the University of California at San Francisco argued that NIH has the greatest expertise for evaluating physical and biological containment of recombinant DNA material and should therefore be the monitoring agency; but their view was in the minority. The NIH Director himself stated that there is "an inherent conflict of interest" in the agency's both sponsoring the research and acting as its "policeman." He also said that NIH has little capability or

experience as a regulator, although it is well qualified to propose standards. Clifford Grobstein, Roy Curtiss, and Frank Young, among others, agreed with Director Fredrickson's recommendation that inspection and enforcement authority be transferred to another agency in HEW, perhaps the Center for Disease Control, with its extensive experience in controlling infectious agents and supervising laboratory practices. Grobstein saw merit in the creation of an independent regulatory commission, but only in the long run, when the implications of genetic manipulations in the areas to extend beyond considerations of health and safety to applications in the areas of energy, agriculture, pharmaceuticals, the environment, and possibly human genetic engineering.

Advisory system

Criticisms of the Recombinant DNA Research Advisory Committee, the authors of the 1976 guidelines and the proposed revisions, also focused on committee members' involvement in recombinant DNA work and their relatively narrow expertise, as well as the National Institutes' failure to encourage broad scientific and public participation in the standard-setting process. According to Jonathan King, among others, the advisory committee has been dominated by biochemists and molecular biologists skilled in the techniques of recombinant DNA and interested in their application but not expert in the assessment of their effects. He charged that scientists with relevant experience in public health, pollution, microbial ecology, and occupational health, for example, had "essentially been excluded from the proceedings." Furthermore, the advisory committee's reliance on unpublished data, communicated by letter and phone call, had contributed to "the abrogation of the normal process of scientific decisionmaking."

Roy Curtiss, a current member of the advisory committee, conceded that "in hindsight, it is clear that the guidelines could have been drafted with much greater public input." To allay the criticisms which would become increasingly deleterious to science and society, he called on the scientific community to "entrust certain decisionmaking authority with representatives of society * * *" by supporting the establishment of two independent advisory committees. One committee, with responsibility for formulating physical and biological containment standards and reviewing applications for approval of host-vector systems, would be composed of scientists in genetics, molecular and cell biology, infectious diseases, epidemiology, ecology, agricultural science, industrial microbiology and other fields that are or might become relevant. A second committee, representative of "all segments of society" and possibly including scientists not engaged in recombinant DNA work, would approve or disapprove but not amend the proposed regulations, suggest how the regulations are to be implemented, and make other recommendations based on a continuing evaluation of the social impact of recombinant DNA technology. Jonathan King endorsed this proposal, particularly its provision for a broadly representative committee to study longer range issues of genetic research and engineering policy.

Role of institutions engaged in research

The NIH guidelines assign primary responsibility for approving the research facilities and procedures and for monitoring compliance

to an institutional biosafety committee. These committees commonly include researchers engaged in recombinant DNA work, other knowledgeable scientists, members of professional school or liberal arts faculties, and, in some instances, public members, although the guidelines do not specify their composition or appointment procedures. In all cases, service is voluntary and in addition to members' other responsibilities.

Nearly all of the subcommittee's witnesses, including representatives of the private sector, supported a provision for onsite review committees, though for somewhat different reasons. Many scientists regard the biosafety committee as an essential instrument of self-regulation, others as a mechanism for employee participation and public scrutiny. Some observers question whether a part-time committee, most of whose members have close ties to the institution and researchers engaged in recombinant DNA work, can be expected to monitor the research carefully and enforce the regulations vigorously. Thus, there is moderate disagreement, not only about the committees' composition but also about their functions and accountability. Harlyn Halvorson, speaking for the American Society of Microbiology, recommended that each biosafety committee include public representatives but have a majority of members with "technical expertise in the activities conducted at the institution in question." King considered it "* * * imperative that laboratory workers be fully involved in decisionmaking processes * * *. Their representatives must sit on biohazard committees * * *." Marshall Shapo observed, from his own experience on the University of Virginia biohazard committee, "* * * It (is) important that we give opportunities for intrainstitutional collegial discussion, and we also * * * provide for some kind of independent review outside of the institution, so that the people who are doing the review are not people who are in any substantial way beholden to those who are doing the research."

Role of State and local governments

In their testimony before the subcommittee, representatives of both the American Society for Microbiology and the Pharmaceutical Manufacturers Association predicated their support of legislation on its preemption of State and local laws imposing greater restrictions on recombinant DNA activities than those provided by the Federal standards. Harlyn Halvorson stated, "It is our fear that if this is not done, we will see a patchwork of conflicting laws regulating microorganisms which recognize no political or geographical boundary * * *. Excessive and variable restrictions would increase the cost of recombinant DNA research and could lead, in many cases, to abandonment of such research." Joseph Stetler of the PMA agreed, "A proliferation of State or local laws and regulations would probably not increase safety, but it could seriously impede the development of the potential benefits of this new technology."

Public interest group representatives were equally insistent that States and localities be permitted to impose stricter standards. Marcia Cleveland of the Natural Resources Defense Council argued that leaving the way open for State and local regulation is essential as an avenue for public participation and political outlet for public opposition. "* * * When citizens are aroused about the hazards of recombinant

DNA, they can respond, and they can respond intelligently." Furthermore, there are many Federal regulatory programs which rely on States to promulgate regulations. "Somehow in each of these we managed to deal with diversity. I see no particular reason why recombinant DNA should pose a greater problem."

The controversy represented by these opposing points of view has seriously impeded congressional action on recombinant DNA legislation and therefore merits careful evaluation. Assuming that there is a strong Federal interest in regulating effectively all recombitant DNA activities in order to protect public health and the environment, the subcommittee has tried to assess whether stricter State and local regulation would seriously impede scientific research and development of beneficial uses of the technology, whether States and localities have demonstrated a strong desire to regulate recombinant DNA activities, whether they have special competence that would be useful, and whether there is a compelling legal or constitutional argument for permitting State and local governments to regulate as they see fit.

The subcommittee has found that while public controversy has flourished in several academic communities and a few States, it has generally not resulted in the passage of legislation more restrictive than the NIH guidelines. Academic and industrial scientists appear to be concerned primarily about proposals to prohibit all recombinant DNA research, prevent the construction of higher containment research facilities, or, on the other hand, restrict all experiments to high containment laboratories. Joseph Grady of Upjohn Co. cited unsuccessful efforts in Cambridge, Mass., to stop construction of a P3 laboratory, while Bruce Levin of the University of Massachusetts referred to a proposal, since rejected by the New Jersey Department of Health, to impose EK2, P3 requirements for all experiments. He commented, "I don't think that is justified * * *. I think that would be an inhibition on scientific freedom of inquiry."

According to other witnesses, the prospects of such actions by State or local governments have become increasingly remote. Paul Berg of Stanford predicted that "* * * the worst that can happen is that a community will say that we want everything to be done under the NIH guidelines." Cetus Corp. president, Ronald Cape, suggested that "* * * some of the pressure for State and local regulation has been motivated in part by a desire to goad Washington into action, particularly since it was felt that the apparent failure of the NIH guidelines to cover industry represented a real problem." And the president of the PMA agreed that there would "not * * * be a lot of enthusiasm in local communities to proceed" once Congress acts to regulate all recombinant research.

Recently passed or proposed city ordinances and State legislation tend to confirm these impressions. In requiring all recombinant DNA experiments to be "undertaken only in strict conformity with the guidelines of the National Institutes of Health * * *," the Berkeley, Calif., City Council noted that "the guidelines are only applicable to NIH-funded research, while many non-NIH-funded private and public research projects continue to be unregulated." (Ordnance No. 5070–NS, October 21, 1977.) Shortly after the subcommittee's hearings, the New Jersey Public Health Council unanimously adopted a

binding resolution that the conduct of artificial recombinant DNA research in the State be carried out under the NIH guidelines. According to the attorney general of New Jersey, the council "chose not to adopt the positions of the public advocate and its own hearing officer regarding any modifications of the NIH guidelines."

An exception is a resolution of the New York Council (No. 1013, August 25, 1977), calling on the Congress "to preserve local autonomy" in the regulation of recombinant DNA research, although the Governor of New York, in vetoing a bill passed by the State legislature, stated that such regulation "should be national in application and not imposed in random fashion from State to State." (Statement of Gov. Hugh Carey, August 12, 1977.)

On the other hand, there are areas of public health where the States have traditionally had regulatory responsibilities and developed some competence. Marc Lappé referred to the California Health Department's supervision of clinical laboratories. In a letter submitted to the subcommittee, the director of the laboratory division of the Connecticut State Department of Health reported that his agency had registered and inspected facilities engaged in recombinant DNA research in accord with the State's public health statutes and regulations. David Newburger, professor of law at Washington University in St. Louis, generalized:

> Under our Federal system of government, the States have a right to protect the health and safety of their citizens, just as the Federal Government exercises some rights in that area on a nationwide basis. Unless there is some compelling national reason for us to distinguish this kind of research from all other research, I cannot see any reason to preempt the area.

Views of the subcommittee

The subcommittee believes that legislation or administrative action to regulate recombinant DNA research should correct the deficiencies of the present system but retain its successful features as well as maintain continuity. In view of the fact that existing statutory authorities are, on the whole, adequate to regulate commercial applications of the technology, no new Federal agency is needed. (See below.) Instead, legislation should assign authority to the Secretary of Health, Education, and Welfare, who will draw upon the expertise of NIH in formulating standards but should delegate monitoring and enforcement responsibilities to the Center for Disease Control or another suitable agency in the Department. The subcommittee agrees that NIH may appear to be compromised by its commitment to supporting recombinant DNA research; nor is it well equipped by previous regulatory experience to perform the latter functions. The subcommittee is concerned that HEW give adequate attention to recombinant DNA research directed toward agricultural, energy, and other nonhealth applications, but believes that no other Federal agency has comparable expertise in the broad range of work with recombinant DNA.

The present membership of the Recombinant DNA Molecule Program Advisory Committee should form the core of an expanded advisory committee to the Secretary, including members with expertise in regulatory procedures, safety and health regulation, and laboratory work. Lay opinion should also be represented. In view of the rapid development of recombinant DNA research, however, the legisla-

tion should not specify the committee's composition in detail. The subcommittee carefully considered Roy Curtiss' proposal to establish two independent advisory committees, but concluded that the technical and social policy aspects of even the physical and biological containment standards or host-vector approval cannot be readily distinguished. Moreover, communication among scientists and nonscientists who advise the Secretary should be encouraged rather than inhibited. The enlarged advisory committee should continue to exercise the functions assigned to the NIH Recombinant Advisory Committee, of recommending changes in the regulations and evaluating host-vector systems submitted for certification.

The subcommittee recommends that the chief administrative officer of any institution, company, or laboratory conducting recombinant DNA research be required to appoint a committee whose members should include scientists not engaged in recombinant DNA work, representatives of laboratory workers, and public members not affiliated with the institution. Again, however, the responsible official should have some discretion in the appointments.

The subcommittee doubts that part-time members of institutional committees will have sufficient time and motivation to monitor experiments regularly and to investigate thoroughly allegations of violations of the regulations. The committee's primary responsibilities should be to approve research facilities and procedures for individual projects, oversee the training of researchers and laboratory workers, and serve as a channel of communications between researchers and the Department of HEW. This role, though more limited than that implied by the current guidelines and proposed changes, is nonetheless essential to insure compliance with the recombinant DNA research standards.

The subcommittee finds that States and localities have generally recognized that compliance with the physical and biological containment standards of the NIH guidelines provides adequate assurance of safety in the conduct of recombinant DNA research. Actions by States and communities to prohibit some or all experiments or to impose higher containment standards than are required by the Federal Government could impede scientific inquiry and the development of beneficial uses of recombinant DNA technology. Congress may preempt State and local regulations that impose such a burden on interstate commerce. On the other hand, the subcommittee recognizes the responsible nature of most State and local government actions to date and the value of informed citizen participation in developing policies governing scientific activities. In addition, observance by researchers of Federal standards is likely to vary among localities and laboratories. Many communities have demonstrated an interest in attempting to insure compliance with the NIH guidelines and have experience in related areas.

For these reasons, the subcommittee recommends a partial Federal preemption of State and local regulation of recombinant DNA research. Under this provision, a State could not by regulation or legislation directly or effectively prohibit experimentation or require physical or biological containment measures exceeding those required by the Federal Government, unless the Secretary of HEW elects to waive

Federal preemption upon the presentation of convincing reasons in support of stricter standards. A State or political subdivision would be permitted to take other actions to assure its citizens that the Federal standards were being observed. These actions include registering and inspecting facilities, requiring public representation on the institutional biosafety committee, investigating alleged violations of applicable regulations, and seeking an injunction to stop a violation. A State would also have standing in Federal court to obtain injunctive relief, pending an investigation and appropriate action by the Secretary, in the unlikely emergency that an activity being conducted in compliance with the regulations were found by the court to pose an imminent threat to the health of laboratory workers or the general public. Finally, a State, community, private organization or citizen should have an opportunity to comment to the Secretary on an application to conduct recombinant DNA research.

PROCEDURES

A large majority of NIH research grants are made to institutions rather than individuals, but it is the principal investigator who bears primary responsibility for compliance with the NIH recombinant DNA research guidelines and can be held accountable for disregarding them. Among other duties, he or she must submit with the grant application to NIH a Memorandum of Understanding and Agreement (MUA), certified by the institutional biosafety committee, and describing the proposed experiment and the procedures and facilities that will be used to achieve the required levels of physical and biological containment. The NIH Office of Recombinant DNA Activities must review and approve or disapprove the proposed MUA before the work can begin. In the event of a violation of these procedures or standards, NIH's only recourse is to deny the use of grant funds for recombinant DNA experiments or halt further expenditures of grant funds if the experiment is in progress. The latter may be an embarrassment to the institution but is a relatively severe sanction for the principal investigator and his colleagues on the project. NIH has taken this action in only one instance, upon discovering that no MUA had been approved, as required, for a project begun before the guidelines were issued.

Witnesses before the subcommittee acknowledged the need to devise new procedures applicable to privately supported research activities. What impressed the subcommittee, however, was the degree of consensus on elements of a regulatory system appropriate to both the academic and industrial sectors. Stetler of the PMA, Halvorson of the ASM, Joseph Keyes of the American Association of Medical Colleges, and OSTP Director Frank Press all advised against licensure of individual researchers as "onerous and burdensome" but recommended a system of Federal licensing of facilities to conduct recombinant DNA work. They said that revocation or suspension of such a license would be an effective deterrent to misconduct. Stetler also proposed the registration of individual research projects with the Federal agency, although primarily for informational purposes. Grady of Upjohn suggested that researchers file the equivalent of an MUA,

which would automatically become effective after 30 days. Press cautioned that:

> The notion that all paths of investigation must be identified and approved in advance flies in the face of the scientific method, in which the results of one step in the process guide the next decision point. . . . A cumbersome review of experimental protocols and the many contingent experiments may prove counterproductive.

Similarly, witnesses generally opposed provisions for seizure of research materials, high fines, or criminal penalties for violations. Several pointed out that civil or criminal fines would impose a greater hardship on academic than on industrial research scientists.

A number of witnesses called for a scale of penalties, each appropriate to a particular offense. When asked what action should be taken in the event of a violation of the containment standards, Oliver Smithies of the University of Wisconsin said that it would be appropriate to revoke the license for conduct of a prohibited experiment or use of an untested organism. A less serious offense might merit closing of the laboratory for a period of time equal to the duration of the violation. With reference to the behavior of individual researchers, David Newburger suggested that:

> . . . the Federal Government through the self-regulatory committees and in consultation with them should ultimately have the power to control the conduct of individuals in the laboratories . . . for example, by having the power to bar a person from working in a laboratory. . . .

In addition to requiring the submission of information on recombinant DNA activities, the Federal Government should have authority to inspect laboratories, according to spokesmen for the pharmaceutical manufacturers and some academic scientists. Levin suggested a sampling of facilities at all four containment levels, while Frank Young of the University of Rochester preferred that inspections be limited to the higher containment laboratories. Jonathan King noted the present difficulty of identifying the biological material used in recombinant DNA work and said that NIH should invest in developing procedures for such monitoring. He also regarded it as essential to monitor laboratory workers' health. In the absence of such records and suitable comparative data, he argued it would be impossible to say what are the health effects of recombinant DNA materials.

Whatever certification, registration, and inspection system is established presents the further problem of public disclosure of normally confidential information. The problem characterizes all business regulation, but it is unusually troublesome when the subject of regulation is basic scientific research with an exceedingly promising technology. Joseph Keyes described the two concerns of the academic research scientist—first, that he may be deprived of the opportunity to exploit his ideas by premature disclosure of a research application or information submitted in compliance with regulatory requirements, and second, that the opportunity to patent an invention and license its development may be lost by premature publication. In the United States, a patent must be applied for within 1 year of publication; in other countries there is no grace period. As a result of the recent Supreme Court decision in *Parker* v. *Bergy*, 46 U.S.L.W. 3788 (U.S., June 26, 1978), the patentability of purified or genetically manipulated living organisms

is in doubt; but if further judicial interpretation or legislation eventually upholds such patent rights, HEW policy would permit grantee institutions to acquire patents and award licenses for recombinant DNA discoveries. As for the private sector, Cetus Corporation President Ronald Cape predicted that the insecurity of patent rights would deter commercial firms from investing in the development of recombinant DNA applications. "(We) will be without a mechanism for useful exploitation of a technology which was invented in this country. It will certainly be exploited elsewhere."

In the absence of statutory protection of the confidentiality of research plans, the Freedom of Information Act (5 U.S.C. 552) would govern their disclosure by the regulatory agency. Subsection (b)(4) of the FOIA provides an exception from mandatory disclosure for "matters that are * * * trade secrets and commercial or financial information obtained from a person and privileged or confidential"; but academic and industrial scientists regard the so-called trade secret exemption as inadequate on several counts. In *Washington Research Project, Inc.* v. *Department of Health, Education, and Welfare* (504 F. 2d 238 (D.C. Cir. 1974)), the court of appeals affirmed a lower court decision ordering release of research grant applications including experimental protocols on the grounds that there were no trade secrets in a "noncommercial scientist's design."

The court further said that "it defies commonsense to pretend that the scientist is engaged in trade or commerce." While that argument would not arise in the case of industrial recombinant DNA research, the interpretations of subsection (b)(4) give little guidance as to the trade secret content of a research design. The leading case, *National Parks and Conservation Association* v. *Morton* (498 F. Supp. 965 (D.D.C. 1974)), applies two tests, of which the relevant one is whether release of the information by the Government agency might cause substantial harm to a competitive position. The Federal criminal statute (18 U.S.C. 1905) barring a Government official's release of proprietary information appears to give little protection because it only applies "unless otherwise provided by law," as in the FOIA.

On the other side of the disclosure controversy are those who insist on public access to all information relevant to the protection of public health and the environment. Marcia Cleveland observed:

> Over the past 10 years . . . this country has come to recognize the importance of citizens having access to the information which . . . forms the basis of government activities that affect our lives. That is what the Freedom of Information Act is about. . . . In the field of recombinant DNA, I don't think that citizens can effectively participate in any sort of regulatory or advisory activity unless they have access to information in the hands of the government . . . and industry.

Cleveland suggested that, if need be, the patent laws should be amended to eliminate the penalty for prior publication. On the other hand, Marc Lappé opposed the granting of any patents for recombinant DNA research discoveries.

Views of the subcommittee

The subcommittee agrees with the admonition of Philip Handler, president of the National Academy of Sciences, to establish only the "minimal arrangements that would suffice to maximize compliance" with the standards governing recombinant DNA research. It has no

desire to create a large Federal bureaucracy of licensing officials and inspectors or to impose on scientists requirements that effectively curtail productive research. On the other hand, accomplishment, prestige, profit, and expectation of benefits for society are positive incentives to proceed as rapidly as possible with the use of recombinant DNA, as with any other promising research technique. Some scientists are already convinced that it poses no significant health or environmental hazard; some may be inclined to substitute their own judgment of safety for that of a regulator. The incidents at the University of California at San Francisco underscore the need for greater accountability.

To support the primary role of the institution in guaranteeing the safe conduct of recombinant DNA research, the subcommittee recommends that the Department of HEW certify individual universities, corporations, private laboratories, or their autonomous divisions to conduct the research. Approval should be conditional upon a showing that the chief administrative officer of the institution has appointed a qualified biosafety review committee thoroughly familiar with the Federal requirements to approve projects and facilities and to provide for the training of investigators and laboratory personnel in proper physical and biological containment methods. The application should describe the facilities and physical containment levels at which the research is planned to be conducted. Further, the institution must agree to monitor the health of laboratory workers and to keep such records and make such reports as the agency prescribes, including reports of any violations of the regulations. The certificate should be valid for the duration of the act or not more than 3 years. If the institutional committee fails to carry out its responsibilities, however, the Secretary should suspend its authority to approve recombinant DNA projects or, where appropriate, specific categories of experiments.

The subcommittee believes that the Department will not have sufficient information to achieve compliance unless privately supported as well as federally funded projects are registered with it in advance. The registration should describe the proposed experiments, the physical and biological containment levels required, the facilities, materials, and procedures that will be used, and other data that the Secretary may prescribe. These projects should not be subject to the rigorous review given Federal research grant applications; indeed it would be appropriate for a project to commence unless the Department raised objections within a brief period of time, such as 14 days. To the extent feasible, qualified institutional or local biosafety officers should be appointed to advise investigators and monitor experiments; but the Secretary should have authority to inspect research facilities and to order the destruction of hazardous or potentially hazardous material prepared in violation of the standards. The Secretary should consider supporting biosafety training programs for investigators and technicians, perhaps conducted on a regional basis.

The suspension of an institutional committee is a severe sanction to be reserved for rare cases of serious dereliction on the part of the institutional officials or their agents. Even the withdrawal of a Federal grant may not be an appropriate response to misconduct by an individual or a small group of researchers. Civil penalties may be ap-

propriate in cases of knowing violations, but the subcommittee also recommends that the Secretary have authority to suspend research being conducted in violation of the regulations and persons from participating in recombinant DNA research for a specified period of time. With regard to both institutional and individual suspensions, the Secretary should be able to issue an administrative order rather than be obliged to seek a court injunction. The judicial route would incur delay and might require a showing of harm or potential harm. Nevertheless, due process must be assured; the more severe the penalty, the more rigorous should be the procedural safeguards.

The subcommittee believes that realization of the benefits of recombinant DNA technology requires some protection of the confidentiality of research ideas and procedures, but it recognizes the public's right of access to information necessary to judge compliance with the Federal standards and their effectiveness in protecting public health and the environment. Unfortunately, the subcommittee has found no ideal balance between these competing values. Two major study commissions have recognized, however, that the disclosure of academic research protocols, submitted in application for Federal funds, is a generic problem, not limited to research with recombinant DNA. Indeed, enactment of legislation to regulate such research would not significantly increase the likelihood of such disclosures. Consequently, the legislation should not establish for recombinant DNA researchers a right of confidentiality which is not accorded to other scientists. Rather, for the time being, HEW should continue its present policy of refusing to disclose a grant application prior to funding and, after consultation with the grantee, of maintaining the confidentiality of potentially patentable information contained in a funded research protocol. In the long run, this policy may entail a heavy administrative burden and possibly further litigation. The appropriate committees of Congress should therefore address the general problem of protecting intellectual property rights, as the President's Biomedical Research Panel and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research have recommended.

Regulation of the use of recombinant DNA techniques would expose the private sector to disclosure of properietary information at the beginning of research and development, whereas present Government regultation of products and processes is limited for the most part to the manufacturing and testing stages. The subcommittee believes that some measure of protection against this risk of disclosure should be provided, especially in view of the fact that recombinant DNA techniques may be only a part of a larger research project. Nevertheless, the concern of the pharmaceutical manufacturers and others is also a general one; they argue that regulatory agency and court interpretations of subsection (b) (4) of the FOIA and 18 U.S.C. 1905 fail to protect much trade secret information, particularly against disclosure to competitors.

The subcommittee doubts that the solution lies in attempting to define in recombinant DNA legislation categories of information, some of which would remain confidential and others be subject to disclosure. Instead, the legislation should establish a notification

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and consultation procedure similar to that followed by NIH in deciding whether to release research protocols submitted by grant recipients.

Recommendations for Regulation of Commercial Applications

As discussed previously, the possible commerical applications of recombinant DNA research are numerous, including the production of pharmaceuticals, pesticides, enzymes, plant growth stimulators, environmental decontaminants, and other materials of value to industry, medicine, agriculture, and the consumer. While some applications of the research may be decades away, others could be available within a few years.

Both the production of large cultures of recombinant DNA organisms to manufacture useful substances and the release of modified hosts or vectors into the environment are contemplated. Congress has the responsibility to insure that any hazards associated with these uses of recombinant DNA techniques for commercial purposes are fully understood and appropriate safeguards are established to prevent any undue risk to human health or the environment. The following section examines a number of policy issues relevant to the applications of recombinant DNA technology. Documents relating to the applicability of current statutes to the regulation of these applications are included in the appendix.

LOCUS OF REGULATORY RESPONSIBILITY

Twelve existing statutes have been identified by the American Law Division of the Congressional Research Service as possible authorities under which to regulate commercial uses of recombinant DNA. (See appendix.) Since a large number of statutes are involved, it has been argued that the most direct way to deal with the problem is to consolidate all of the regulatory authority within a single agency and a single authority. In fact, some legislation (for example, S. 1217) would effectively preempt all Federal statutes except the Occupational Safety and Health Act (29 U.S.C. 631, et. seq. (OSHA)), and lodge responsibility for the regulation of all recombinant DNA activities with the Secretary of Health, Education, and Welfare or an independent commission. Thus, whether or not a recombinant DNA application is pesticidal (now subject to the jurisdiction of the Environmental Protection Agency), for industrial purposes (also largely in EPA's jurisdiction), pharmaceutical (Food and Drug Administration's jurisdiction), or involves the transportation of hazardous materials (Department of Transportation's jurisdiction), sole regulatory responsibility would be vested in a single agency.

While a consolidation of authority appears to be in the interest of administrative efficiency, it would duplicate expertise and responsibilities now existing within other agencies of Government. For example, if an agency or commission were given jurisdiction over a proposed use of recombinant DNA to control insects on agricultural crops, this grant of authority would duplicate the function and expertise of EPA under the Federal Insecticide, Fungicide, and Rodenticide Act—7 U.S.C. 135, et seq. (FIFRA). Similar duplica-

tion would occur with respect to transportation, waste disposal, and other problems that may be associated with recombinant DNA applications and for which expertise and regulatory responsibility have already been established. The types of regulatory problems presented by recombinant DNA may differ, however, from those of conventional materials regulated under existing laws and require specialized training or additional personnel familiar with the scientific aspects of recombinant DNA. Nonetheless, with the exception of regulation of research activities for which HEW currently has primary responsibility, consolidation of all authority in the Department of HEW or an independent commission would require creating a new administrative structure and assembling the expertise to deal with the large number of potential applications of recombinant DNA technology.

APPLICABILITY OF EXISTING STATUTES

Given the speculative nature of the eventual uses of recombinant DNA research, it is difficult to identify precisely the different kinds of public health and environmental problems that may arise. Nonetheless, some observations are appropriate. There are a number of substances which may require control as recombinant DNA technology becomes commercially feasible. While many of these materials may present little or no hazard in and of themselves, the ability to control their production, movement, and use in recombinant activities may be important control mechanisms. Included are the recombined DNA molecules, the enzymes necessary to split DNA molecules and to recombine them, DNA segments to be inserted in host DNA molecules and the organisms serving as hosts for insertion of recombined DNA. The authority should also exist to control substances produced by recombinants.

With the exceptions noted below, all of the materials associated with recombinant DNA applications are apparently subject to one, and possibly several, statutes designed to protect health and the environment. If the material produced, either an organism or a product of an organism, is to be used as a pesticide, the terms of FIFRA apply. Pharmaceutical products and manufacturing processes are subject to the Federal Food, Drug, and Cosmetic Act—21 U.S.C. 301, et seq. (FDCA). To the extent that the substances necessary to produce pesticide products or products subject to the FDCA are not covered by those statutes, they are covered by the Toxic Substances Control Act—15 U.S.C. 2601, et seq. (TOSCA). Similarly, Federal laws relating to water pollution, waste disposal, air pollution, occupational safety and health, and communicable disease all appear applicable to recombinant DNA materials and organisms if they are related to those types of hazards. The extent to which these statutes provide adequate regulatory authority merits closer examination.

There is substantial question regarding the control of organisms containing recombined DNA under TOSCA. This is particularly important when examining requirements for premanufacturing review of organisms which are not pesticidal or subject to the FDCA. For example, attempts may be made to improve the efficiency of sewage

treatment microflora, confer nitrogen-fixing capability on food plants, or accelerate the production of methane or hydrogen by micro-organisms from hydrocarbon sources such as garbage and waste oil.

TOSCA may be capable of embracing organisms containing recombined DNA by virtue of the coverage by that act of DNA molecules. Section 3(2) defines a chemical substance subject to the act as "any organic or inorganic substance of a particular molecular identity." The definition also includes "any element or uncombined radical." It is thus clear that DNA molecules or segments of DNA molecules are fully subject to the provisions of TOSCA, including the premanufacturing notice provisions of section 5.

The authority contained in TOSCA enables the Administrator of EPA to extend controls to any "commercial use" of those molecules, presumably including their use in organisms. For example, EPA would prohibit or limit the commercial "use" of a recombined DNA molecule in an organism that would present unreasonable risks to health or the environment. While this may provide some authority over the organisms themselves, EPA concludes that TOSCA is not meant to control organisms directly. EPA would thus not impose restriction on organisms, only on molecules that might be inserted into them. EPA does not question the coverage by TOSCA of DNA molecules or segments of DNA. Nonetheless, in the absence of specific authority addressing the recombinant DNA question, EPA has committed itself to utilizing the authority under TOSCA to the fullest extent necessary to prevent undue risk to health and the environment. (See Appendix.) Clarifying the authority to reach organisms utilized in recombinant DNA activities would also insure that those persons purchasing DNA recombinants from a producer for the purpose of further cloning would also be regulated to insure no undue risk to health or the environment.

Section 361 of the Public Health Service Act (42 U.S.C. 264) provides the Secretary of Health, Education, and Welfare with authority to prevent communicable disease. In relevant part, section 361 authorizes the Secretary to "* * * make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the states or possessions, or from one state or possession into any other state or possession * * *"

Because of the broad discretion given the Secretary, it has been argued that section 361 provides sufficient authority to control the commercial applications of recombinant DNA. In fact, the Environmental Defense Fund and the Natural Resources Defense Council petitioned the Secretary of HEW on November 11, 1976, asking him to impose control over all recombinant DNA activities under section 361 of the Public Health Service Act. An important issue in the use of section 361 of the Public Health Service Act, or any other statute whose primary purpose is to protect public health, is the extent to which environmental concerns may also be addressed. While environmental concerns often manifest themselves as public health problems, there are other ecological insults, such as the destruction of wildlife habitats or the despoilation of wilderness, whose "public health" link is tenuous. The National Environmental Policy Act (42 U.S.C.

4321, et. seq. (NEPA)), requires in part that all agencies shall insure "* * * that presently unquantified environmental amenities and values be given appropriate consideration in decisionmaking along with economic and technical considerations. * * *" (sec. 102(2)(B)). It has been argued that NEPA requires agencies to protect the environment in actions taken, whether or not the authorizing statute specifically provides for environmental protection. Thus, once an agency has established jurisdiction over a substance for whatever purpose, then it is automatically obligated in its actions to protect the environment.

The extent to which NEPA imposes an additional substantive duty upon each Federal official to protect the environment has not been extensively litigated. Nonetheless, in three important cases (*Calvert Cliffs* v. *AEC* (2 ERC 1779), *Zabel* v. *Tabb* (1 ER 1449), and *EDF* v. *Matthews* (8 ERC 1879)) the courts have upheld the authority and responsibility of agencies to protect the environment, notwithstanding an authorizing statute which does not explicitly provide for environmental protection.

While the authority of section 361 is broad and arguably could reach many, if not all, of the commercial applications of recombinant DNA research, it is highly unlikely that the Secretary of HEW will use the authority in this manner. In the absence of definitive judicial rulings, using section 361 of the Public Health Service Act to safeguard the environment could result in litigation.

PREVENTION OF HAZARDS

With the passage of TOSCA in October 1976, Congress established the principle that chemical hazards should be controlled before their hazards become manifest. The act's mechanisms for premarket review, which were in part patterned after similar provisions in pesticide and drug law, provided the first comprehensive means of enabling regulators to review hazards and take action before a substance reaches the channels of commerce. Experience in recent years with such chemical disasters as PCB, kepone, PBB, vinyl chloride, and others demonstrated that the Nation could no longer afford to act against chemicals after the damage was done. In his environmental message of April 1977 President Carter reiterated this policy and stated emphatically that the administration embraces preventive control. The reasoning that resulted in the preventive control measures in TOSCA and other statutes applies as well to commercial products developed with recombinant DNA techniques.

Apart from FIFRA and the FDCA, the only statute explicitly providing for premanufacturing review is TOSCA. The premanufacturing review coverage of TOSCA is broad, excluding only pesticides, tobacco and tobacco products, nuclear material, firearms, materials subject to FDCA, and mixtures of chemical substances. While other statutory authorities, like section 361 of the PHS Act, may also be interpreted to provide this type of authority, the explicit terms of TOSCA provide for premanufacture review of new chemical substances and significant new uses of existing ones. However, the limitations of TOSCA described above relative to the coverage of recombinant DNA

organisms also apply to the premanufacturing review provisions of the act. Nonetheless, since the commercial manufacture of new molecules, including the manufacture of new DNA molecules, requires premanufacturing review under TOSCA, some further discussion of its provisions is appropriate.

Under section 5 of TOSCA, manufacturers of new chemical substances (in this case, new DNA molecules) are required to give notice to EPA 90 days prior to the first manufacture of those substances. Significant new uses of existing substances are also covered by the same provision. The premanufacturing review period may be extended to 180 days if the Administrator finds good cause. The premanufacturing notice must include: (*a*) the identity of the substance, (*b*) the proposed uses, (*c*) the amounts to be produced, (*d*) a description of byproducts, (*e*) employees exposed, and (*f*) the manner or method of disposal. The results of any tests which have been conducted on the substance must also accompany the submission.

During the premanufacturing review period, the Administrator of EPA is authorized to halt or limit the manufacture of the new substance or significant new use of an existing substance if the Administrator finds an unreasonable risk of injury to health or the environment. In addition, mechanisms exist to halt or limit the manufacture of the substance if the information available to the Administrator is insufficient to permit a reasoned evaluation of the health and environmental effects, and the Administrator makes a determination that an unreasonable risk exists or that there will be significant human or environmental exposure.

While TOSCA provides for premanufacturing review, manufacturers are free to proceed if the Administrator fails to take action during the premanufacturing review. There is substantial question as to whether this type of "catch me if you can" procedure is sufficient to guard against potential dangers of recombinant DNA exposure. Premanufacturing review and certification by the Administrator that no undue risk to health or the environment exists, as is now the case with pesticides and drugs, appears to be warranted.

FIFRA requires premanufacturing approval of pesticides by EPA. In order to obtain approval, a manufacturer must demonstrate to the Administrator that the pesticide will perform its intended function without unreasonable adverse effects on the environment, including humans. If a manufacturer is unable to demonstrate an absence of unreasonable adverse effect, it is the intent of this statute that registrations not be granted. While the EPA has been criticized for failing adequately to screen pesticidal products prior to registration, it is clear that this procedure, if exercised correctly, can serve as a basis for eliminating undue risk to health or the environment associated with the pesticidal uses of recombinant DNA techniques prior to any manufacture, sale, or movement in commerce. A similar procedure exists under the FDCA with respect to food additives, color additives, new drugs, new animal drugs, devices, and pesticide residues. A major shortcoming of the FDCA is that the regulatory authority extends only to the protection of human and animal health, not to the protection of the environment.

In summary, with respect to (*a*) substances subject to FDCA, (*b*) pesticides, and (*c*) substances subject to section 5 of TOSCA, it is

clear that Congress intended that materials not be approved for use until risks are identified and judgments made on the extent to which those risks can be tolerated. Very few, if any, of the commercial uses of recombinant DNA technology should escape the premanufacturing review provisions of these three statutes.

A necessary adjunct to any mechanism for premanufacturing review is the authority to take regulatory action where there is cause for concern but no irrefutable evidence of injury. While this principle is embraced in most statutes controlling hazardous materials, it is particularly important when controlling risks associated with recombinant DNA applications since we know far less about their effects on health and the environment.

After a recombinant DNA molecule or organism has been approved for use and manufacture has begun, generally a greater degree of risk must be evident in order to take action, in part because the economic effects of regulation are greater. While in theory an absence of assurance of safety of a pesticide or drug should result in withdrawal of its approval, action is rarely taken unless positive indicators of risk are developed from test data or other evidence. Nonetheless, it is clear that evidence of actual injury, as opposed to risk, need not be demonstrated. Recent cases in environmental law support this conclusion.

The major exception appears to be in standards established for the protection of worker health under OSHA. The authority of the Secretary of Labor under that act is limited to recognized hazards to the working environment. In *American Mining and Refining Company* v. *The Occupational Safety and Health Review Commission* (501 F. 2d 504 (1974)) the court ruled that the regulatory authority under that act covers only airborne contaminants known to be dangerous. Whether OSHA's authority extends to unquantifiable and speculative dangers is thus questionable. (See Appendix.)

Under TOSCA, the Administrator of EPA is required to exercise his authority to the extent that risks may not be prevented or reduced to a sufficient extent by actions under Federal laws not administered by EPA (section 9(a)). Since actual injury need not be shown in order to take action under TOSCA, EPA has the authority and responsibility to protect worker health if the authority of OSHA is insufficient.

CONTROL OF MANUFACTURE

The previous discussion has focused largely on the authority of existing statutes to control the products of recombinant DNA research following their manufacture. An equally important consideration is whether existing statutes are sufficient to control hazards that may arise in the process of production and expose those inside or outside the facility to risks. While certain statutes, such as the Clean Air Act and the Federal Water Pollution Control Act, provide control over waterborne effluents and airborne emissions, the authority of these statutes does not extend to specifying the manner of production in order to avoid the effluent or emission. Likewise, OSHA gives the Secretary of Labor authority to establish environmental standards within the workplace but does not give the Secretary authority to specify the manner of production of any substance.

Of the three principal statutes which might be used to control the commercial products of recombinant DNA technology (FIFRA, TOSCA, and FDCA), only the FDCA may contain sufficient authority to insure that products subject to that act are manufactured in a safe manner. Section 701(a) gives the Secretary of HEW authority to issue general rules for the efficient enforcement of the act. This broad grant of authority may be sufficient to reach the manufacture of recombinant DNA.

FIFRA, while providing ample authority to protect against hazards associated with the products of manufacture, contains no authority which would enable the Administrator of EPA to impose requirements with respect to the manner of manufacture. Likewise, TOSCA, while providing broad authority to deal with recombinant DNA molecules and other chemical substances, contains only limited authority to specify the manner of manufacture. Section 6(b) of TOSCA enables the Administrator to order that quality control procedures be invoked in the event a chemical substance or mixture is manufactured or processed in a manner which unintentionally causes it to present unreasonable risks to health or the environment. In addition, in imposing quality control procedures, the Administrator is required to undertake a potentially time-consuming and laborious adjudicatory procedure in order to impose requirements. While other statutes, such as section 361 of the Public Health Service Act and perhaps the plant and animal quarantine laws, may be construed to provide this kind of authority, an explicit statutory declaration of the authority would be desirable.

Many of the problems associated with manufacture are similar to those associated with conducting research with recombinant DNA molecules. The scale is larger and, arguably, the opportunity for environmental damage is greater in manufacturing situations than in research because of differences in personnel training, volume of materials used, and methods of production. Nonetheless, the types of controls necessary to protect workers in the environment and commercial manufacture are similar to those that may be imposed in the laboratory.

Hazards to health and the environment that may occur after commercial manufacture present different problems that must be addressed separately. While tests to determine health and environmental effects may be similar, the control mechanisms developed to prevent hazards in transportation, use, and disposal of the material will be very different in character than those applied inside the laboratory or manufacturing plant. The latter controls will be characterized largely by biological and physical containment requirements similar to those in the NIH guidelines and future regulations governing experimentation.

TESTING REQUIREMENTS

It is implicit in any premanufacturing review system that decisions to approve the manufacture of recombinant DNA or derived products will be made intelligently with as full knowledge as possible of the risks. This means that test data relating to health and environmental effects must be available in the premanufacturing review

process so that these decisions are made properly. It is also implicit in any system for premanufacturing review that the responsibility for developing tests with respect to health and environmental effects should lie with those who will benefit economically from the commercialization.

Moreover, authority should exist to order testing after premanufacturing review in order to insure that health and environmental data is current. There have been important improvements recently in the design of test mechanisms for health and environmental effects of chemical substances and other materials. The development of rapid screening systems, including the so-called Ames test, for mutagenesis and possible carcinogenic activity is but one indication of progress in hazards testing technology. The availability of testing authority should help insure that the latest in testing technology is used fully.

Each agency of Government with regulatory responsibility applicable to recombinant DNA technology and related products also has research authority or access to it. In addition, TOSCA contains authority for the EPA Administrator to require testing by manufacturers and processors of chemical substances, which could include recombinant DNA and other derived products. The testing authority of TOSCA is broad and requires the Administrator to order testing when there is insufficient information or when a substance will be produced in substantial quantities. Congress intended that the provision be broadly interpreted: the conference report accompanying TOSCA indicates that testing may be required whenever "there is a basis for concern." (Senate Report 94–1302, 94th Congress, second session, page 61.) This authority appears to be sufficient, although the task is complicated by the fact that it may be very difficult to design tests to determine potential health or ecological impacts of a unique new organism.

RECORDKEEPING AND REPORTING REQUIREMENTS

Section 8(a) of TOSCA provides comprehensive authority for the Administrator of the EPA to require recordkeeping and the submission of reports concerning a broad range of activities associated with the commercialization of chemical substances. Information that may be required includes the identity of the substance, categories of use or proposed categories of use, the amount produced, any byproducts resulting, existing data concerning environmental and health effects, human exposure, and the manner or method of disposal. The authority contained in section 8(a) is limited, however, by an exemption for small business from the general reporting requirements. As a substantial number of producers of commercial recombinant DNA could well fall within most definitions of "small business," the limitation of section 8(a) could be detrimental.

Section 8 (c), (d), and (e) requires producers and distributors to maintain records of adverse reactions, to maintain lists of health and safety studies conducted, known, or reasonably ascertainable with subsequent submission upon request by EPA, and notice to the Administrator of substantial risks associated with substances. The small business reporting exemption does not apply to section 8 (c), (d), and (e).

Other statutes providing for the regulation of recombinant DNA also have separate recordkeeping and reporting requirements. While certain statutory authorities, such as section 361 of the Public Health Service Act, do not explicitly provide for reporting and recordkeeping, these requirements are presumably within the discretion of the Secretary. To the extent that other statutes provide for recordkeeping and reporting, the Administrator of EPA is admonished in section 8(a) of TOSCA not to impose requirements which are "unnecessary or duplicative." As Jonathan King pointed out in the subcommittee hearings, however, there are presently no techniques for tracking inadvertent contaminations for adverse health or ecological effects.

Views of the subcommittee

In examining the anticipated uses of recombinant DNA technology, the subcommittee recognizes the limits of present knowledge. Neither the course of research and development nor the progress of risk assessment can be predicted with accuracy. It may be, as Roy Curtiss suggested, that commercial uses of genetically modified micro-organisms will pose no threat to public health or the environment. On the other hand, the risks of large-scale production and release of recombinant DNA organisms may be greater than those attributed to experimentation in research laboratories.

Congress and the executive branch should anticipate these potential hazards before they materialize. With that in mind, the subcommittee has studied existing statutes to determine whether they are capable of insuring the safe manufacture, processing, use, transportation, and disposal of recombinant DNA products. There should be adequate provisions for premanufacturing or premarketing approval, quality controls in manufacture, testing of effects, recordkeeping and reporting, and appropriate packaging and handling. With the exceptions noted above, the subcommittee has found surprisingly few obvious gaps in these authorities; effective regulation, however, depends upon their proper administration.

The subcommittee believes that Federal regulation should focus on the nature of the prospective uses of recombinant DNA techniques rather than on the technology per se. It therefore makes little sense to create a new agency or bureaucracy to regulate all activities involving recombinant DNA when existing agencies have appropriate authority and expertise in controlling a variety of chemical hazards, insuring drug safety, regulating waste disposal and transportation of hazardous materials, and performing similar functions. Thus, authority over pesticidal uses of recombinant DNA technology should remain with the Environmental Protection Agency. Regulation of pharmaceutical and other applications subject to the Federal Food, Drug, and Cosmetic Act should remain with the Food and Drug Administration. The same reasoning applies to transportation and plant and animal protection. Legislation relating to research should not preempt existing authorities that are applicable to commercial uses of recombinant DNA. There is a danger, however, of conflicting regulation by different agencies. In the case of university and industrial research activities, this danger is minimized by the limitations mentioned above in the Occupational Safety and Health Act,

the Food, Drug and Cosmetic Act, and the Toxic Substances Control Act. With respect to commercial activities beyond the research stage, however, the likelihood of overlapping regulation is much greater. The subcommittee urges close coordination among the relevant executive agencies; memoranda of understanding or Executive orders may be appropriate methods of sorting out their responsibilities. The executive branch should begin at once to make these determinations. To the extent that reorganization of the executive branch consolidates jurisdiction over matters of health, safety, and environmental protection, authority over commercial applications of recombinant DNA should also be consolidated.

The subcommittee further recognizes that certain agencies may need to acquire expertise in recombinant DNA techniques and additional personnel and other resources. For example, the Environmental Protection Agency will likely assume much of the burden for screening and controlling recombinant DNA molecules and their uses. Depending upon how rapidly the technology is developed, EPA should be given additional funds and manpower as necessary to administer the program.

Finally, existing statutory authorities should be used to the maximum extent feasible. There is broad discretion in several statutes, including section 361 of the Public Health Service Act and the plant and animal quarantine laws, to protect public health and, to an uncertain degree, the environment. Careful consideration should be given to using those authorities to remedy weaknesses in other Federal laws more directly related to recombinant DNA applications. It is particularly important that recombinant DNA organisms intended to be released into the environment be subject to premanufacturing review and certification that they pose no significant risk. If authority to accomplish this is questionable or extensive litigation likely, Congress should consider amendments to the relevant statutes. The executive branch should make these determinations as soon as possible and propose appropriate legislation to Congress.

MINORITY VIEWS OF SENATOR HARRISON SCHMITT

I cannot agree with the general thrust toward the excessive regulation of a form of basic scientific research that is inherent in the majority's recommendations. The suggested risk cited for recombinant DNA research is purely theoretical and hypothetical. This suggestion is not supported by our knowledge of recombinant processes that have occurred in nature since life began billions of years ago or by other scientific considerations.

Many of the conclusions and recommendations made by the majority are unwarranted and not supported by the weight of the testimony presented during the 3 days of hearings held by the Science, Technology, and Space Subcommittee. Because of the debilitating effect that over-regulation of basic research would have on all science and technology in the United States, the following dissenting views are offered for the benefit of committee members and others.

GENERAL CONSIDERATIONS

At the outset, it is important to emphasize that the potential risk surrounding research with recombinant DNA molecules was brought to the public's attention by the specific group of research scentists involved in such research. This was done at a very early stage in our understanding of recombinant processes. The end result was the creation of the present National Institutes of Health (NIH) guidelines governing publicly funded DNA research. This is an aspect of the recombinant DNA controversy that should not be ignored, for it demonstrates both a high level of professional responsibility and the fact that the system can work without unnecessarily restrictive regulations. (See attachment A.)

Moreover, it is significant that some of the scientists who first called attention to the conjectural hazards, after more research and after consultation with scientists in related disciplines, have since reassessed the situation and changed their perception of the risk. (See attachment B.) The NIH is presently considering proposed revisions to the guidelines that would have the effect of further relaxing the standards to take into account this new understanding. These factors demonstrate the preliminary nature of our knowledge in this relatively new field of scientific inquiry. Any actions taken by the Congress or the executive branch should be considered as an interim measure until further information is obtained from which we can make an accurate assessment of the hazards, if any, associated with such research.

The use of recombinant techniques to modify fundamental genetic material offers great promise for all mankind through improved understanding of biological processes, and varied applications in such fields as medicine, production of enzymes for industry, and agriculture. It is now one of our foremost weapons in the search for an inexpensive

prevention or cure of cancer as an alternative to increasingly expensive treatment. The testimony of several witnesses indicated that the first real benefits from practical applications of recombinant DNA research are not far off and may be only the beginning of a vast new capability to benefit mankind. Major breakthroughs have already been achieved with the structural genes that specify insulin (used in treatment of diabetes) and the protein somatostatin, which has been described by Dr. Philip Handler, President of the National Academy of Sciences, as a "scientific triumph of the first order" because of its significance for the understanding of the structure and function of the genetic apparatus.

Nevertheless, as with any new field of scientific research, it is impossible at this stage to say with absolute certainty that there are no future hazards attendant to such research. To date, however, there have been no illnesses or other harm associated with recombinant DNA research. Hearing testimony made it clear that there have been recombinant processes occurring in nature since life began, and nature has built-in defenses against aberrant DNA strains. (See attachment C.) However, we cannot ignore the theoretical risks and the necessity to take all reasonable steps to protect the health and safety of the public and the environment until further evidence is accumulated. The continued emphasis of the NIH guidelines in public and commercial activities is clearly justified at this time.

There is a need for Congress to play an active role in the discussion and formulation of Federal science policies with respect to the conduct of recombinant DNA research. The Science, Technology, and Space Subcommittee has acted, and should continue to act, to fulfill its responsibility for science and technology policy oversight. The hearings held by the subcommittee on this issue were conducted pursuant to its broad jurisdiction over "science, engineering, and technology research and development policy." Chairman Stevenson is to be commended for his efforts to ensure that legislation was not passed prematurely and for holding the hearings on recombinant DNA and related science policy issues suggested by the minority. The testimony presented at last fall's hearings provides valuable insight into the hypothetical nature of the risks and the potential benefits associated with recombinant DNA research and its applications.

The potential risks and benefits of regulation of scientific research were also explored during the subcommittee hearings. However, there is a need for further study and evaluation of the implications of regulation for all research in basic science and technology. The recombinant DNA controversy is particularly significant since policy decisions made with respect to the conduct of recombinant DNA research and technology could significantly impact other aspects of scientific research and development. For that reason, it is essential that we move cautiously and fully explore all of the implications that could result from its statutory regulation.

REGULATION

My objections to the majority report cover both the scope and impact of its regulatory recommendations. In recommending a broad

regulatory structure, the majority report ignores the broad science policy aspects of the issue. We must address several broad science policy questions before recommending the regulation of recombinant DNA research. For example:

—What is the impact of various regulation alternatives of science and technological development and innovation?

—What is the appropriate role of the scientific community, of the public, of the Congress, etc., in the regulation of basic scientific research?

—What are the appropriate mechanisms and forms for efficiently resolving conflicts and formulating science policies?

—To what extent should the public participate directly in the formulation of science policies, and what should be the role of the State and local governments in the formulation of such policies?

—To what degree is there a constitutional guarantee of freedom of scientific inquiry, and under what conditions may it be abridged?

—What will be the consequences of regulation on the activities of other nations and on our competitive economic position relative to them?

These and other questions relating to the social, legal, political, and ethical implications of regulating scientific research must be addressed. To that end, I have introduced a bill, S. 2267, The National Science Policy Commission Act, designed to provide a mechanism for a comprehensive, 2-year reassessment, clarification and analysis of Federal science policies regarding potentially hazardous research activities. Under the bill, a national commission would be established to study and report to the Congress with respect to its findings, conclusions, and recommendations regarding Federal science policies.

Although it may be that there are alternatives to a commission of the sort as envisioned by S. 2267, the need for some mechanism to assist the Congress in the development of broad science policies is clear. It is essential that there be broad and varied participation by representatives of all sectors of the economy in the policy formulation process. I am hopeful that the subcommittee will continue to explore these issues in the following months.

If the Congress should take the unfortunate action to regulate recombinant DNA research, such regulation at least should be flexible and interim in nature. The majority report recommends that legislation extend for at least 3 years to allow sufficient time to assess the effect of Federal standards. Research with recombinant DNA molecules is a unique field in which major scientific breakthroughs have been achieved in a relatively short period of time. Our knowledge of recombinant processes has increased many fold in the past several years. It would not be unrealistic to expect a continued growth in our understanding of the risks and benefits associated with such research as our laboratory experience grows. Unnecessarily restrictive Federal standards could seriously impinge upon our Nation's research efforts and unfavorably alter the course of scientific progress and development. Legislation, if passed, should expire no later than 2 years from the date of enactment. Subsequent review and analysis based upon an improved understanding of the nature of the risks and the effect of Federal standards would determine if there was truly a need for any legislation.

PREEMPTION

One element of science and technology policy, and a central element of proposed recombinant DNA legislation, concerns the degree of public participation in the policymaking process. At issue is the extent to which Federal legislation should preempt State or local government action with respect to regulated activities. The majority report recommends a "partial" Federal preemption of State and local regulation which would in effect prohibit State or local governments from enacting stricter standards that the Federal Government unless "convincing reasons" are shown.

At the subcommittee hearings, the scientific community testified strongly in support of the need for Federal preemption in order to achieve uniform standards. On the other hand, it must be recognized that any form of Federal preemption represents an encroachment on the rights of State and local governments and restricts the traditional right of the public to act to protect the public health and safety. A delicate balancing process is necessary to assure that States have the right to regulate research activities conducted within their borders while at the same time avoiding an unnecessary patchwork of conflicting local regulations. It is encouraging to note that the scientific community and local governments appear to be working out satisfactory arrangements on their own once they began to communicate with each other rather than confront each other.

National decisions made with respect to recombinant DNA research activities will have implications for other areas of science and technology. For example, a similar controversy surrounds the subject of nuclear waste management and the rights of States to prohibit permanent disposal of radioactive wastes within their borders.

In any case, the step to preempt State and local action is a serious one which should not be taken without a full understanding of its implications. I am not satisfied that we possess the necessary information at the present time. There is a need for further study of the appropriate roles of the public, and State and local governments, and the effects of preemption. Whatever is ultimately decided, there must be adequate provision for public and congressional participation in science policymaking.

SECTION 361 OF THE PUBLIC HEALTH SERVICE ACT

I am extremely disturbed by the language in the majority report which suggests that extension of the NIH guidelines to the private sector could be accomplished by regulatory action under the authority of section 361 of the Public Health Service Act (PHSA, 42 U.S.C. 264). The majority report recommends that the Secretary of Health, Education, and Welfare (HEW) reconsider using the authority of the PHSA if Congress does not act on legislation. Further, the report recommends that the Federal Government rely upon the "full legal authority" in extending the guidelines, and states that the subcommittee is "not persuaded that the legal obstacles to use of section 361 of the Public Health Service Act are insuperable." While the majority concedes that it has not reached a final judgment on the legal issues relat-

ing to the use of section 361 to regulate recombinant DNA research, they nonetheless recommend that the Secretary of HEW "give the most serious consideration" to promulgating standards under section 361 if the legislative committees conclude the existing authority is adequate. The majority report also suggests that the Secretary prepare for the use of section 361.

The effect of these statements, in my view, is to give unjustified and ill-advised support to the use of section 361 to regulate recombinant DNA research in lieu of legislation. At this time, I am opposed to any language in the report that might suggest that the subcommittee considers section 361 to be appropriate for regulation of recombinant DNA research.

The majority's recommendations regarding section 361 are somewhat surprising inasmuch as the applicability of that statutory authority to recombinant DNA research was not a subject of the hearings held by the subcommittee. The only reference to that section during the entire course of the hearings on recombinant DNA research was made by Dr. Gilbert Omenn of the Office of Science and Technology Policy. Dr. Omenn expressed the opinion that regulation by invoking a law designed to protect against contagion would amount to overkill. There is no support in the hearing record for application of section 361 of the PHSA to recombinant DNA research.

The majority apparently has been persuaded by subsequently acquired evidence that application of section 361 would be appropriate. I am not so convinced. In fact, information presently available indicates many problems associated with use of this section to control recombinant DNA research.

As the majority report acknowledges, section 361 refers only to "communicable diseases" affecting human beings. Its application to plants, animals, or the general environment is questionable at best. Clearly, section 361 was not intended by Congress to apply to basic scientific research activities such as with recombinant DNA. Support for this conclusion can be found in the report of the Federal Interagency Committee on Recombinant DNA Research and a response from the Congressional Research Service (CRS), both of which agree that "no single legal authority or combination of authorities currently exist that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements." (See attachment D.)

Moreover, there is some question as to the application of section 361 to activities of a purely intrastate character. The most recent court decision construing section 361 ruled that the scope of this section extends to intrastate activity where necessary to prevent the interstate spread of disease. (*State of Louisiana* v. *Mathews*, 427 F. Supp. 174 (1977)). With reference to DNA research, there is no evidence to support the position that intrastate regulation is necessary to prevent the interstate spread of communicable disease. Any hazards arising from recombinant DNA research are at this time purely speculative and highly unlikely.

The Department of HEW has stated on several occasions that it prefers legislation, and that the use of section 361 to regulate recombinant DNA activities would be both inappropriate and inade-

quate. (See attachment E.) Because of my concerns over the possible application of section 361, I wrote to the Secretary of HEW on May 4, 1978, asking for his views on the scope and nature of authority included under section 361. (See attachment F.) The Secretary's formal response has yet to be received.

In response to a similar inquiry, the Director of OSTP acknowledged that use of section 361 to regulate recombinant DNA research could create problems because (1) it acknowledges a significant risk of transmission of communicable disease, (2) it creates precedent for broad intrusions into the research environment, and (3) it does not apply to hazards to the environment that have no effect on human health. (See attachment G.)

At the very least, application of section 361 to recombinant DNA research would be subject to legal challenge. Section 361 has been employed in the past exclusively to regulate known human disease organisms, as well as known carriers of these organisms. There is no legal precedent supporting the application of section 361 to purely hypothetical risks. Given the complexity of the issue, use of section 361 is likely to generate litigation which would further cloud the status of legislative and administrative efforts.

I am also concerned about the scope of regulatory authority granted to the Secretary of HEW under section 361. On its face, it would grant to the Secretary unbridled discretion to promulgate and enforce such regulations as he deems necessary, and to take other measures necessary to carry out the regulations. There are no apparent restrictions in the law on the power of the Secretary nor are there procedural requirements that he must follow in implementing and enforcing these standards. It is my fear that by encouraging action by the Secretary of HEW to regulate a form of basic scientific research under an unusually broad grant of authority without a specific and clear mandate, we could unwittingly be initiating a dangerous regulatory precedent for all basic science and technology. It is especially unsettling that this broad discretion would be given to the Department of HEW, the largest and most bureaucratic regulatory entity in the world. Under these circumstances, I cannot agree with the conclusion implicit in the majority's recommendation that it would be preferable to avoid legislation if the Secretary can be persuaded to act under section 361.

There are numerous other deficiencies with the recommended use of section 361. Violations of section 361 would be punishable under section 368(a) of the PHSA by a fine of not more than $1,000 or by imprisonment for not more than 1 year. This is extraordinary punishment for violations of rules governing hypothetical and unproven risks. There is no sunset provision or other similar provision limiting the duration of any regulations or other action taken by the Secretary pursuant to section 361. There is no Federal preemptive authority under this section. The authority of the Secretary in relationship with other Federal laws would not be specified. It would not contain Administrative Procedure Act or National Environmental Policy Act waivers for initial promulgation of the NIH guidelines as regulations. Section 361 would not authorize the Secretary of HEW to waive regulatory requirements for activities that pose no significant risk to health or the environment. In view of all these deficiencies, the

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majority's recommendations concerning section 361 are without significant merit.

Recent events, however, suggest that increased attention will be focused on the use of section 361 in lieu of legislation. Based on presently available information, it would be unwise for this subcommittee to condone or support the use of such inadequate statutory authority, especially in such a delicate matter as the regulation of basic scientific research. If there is shown to be a need for statutory authority to ensure compliance with the NIH guidelines by the private sector, it should be accomplished by specific legislation expressing the clear intent of the Congress rather than unilateral action by the executive branch.

SUMMARY

I am greatly disturbed with the substance and implications of the majority's recommendations which results in unwarranted and excessive regulation of a field of scientific research where the risks are purely theoretical, inconsistent with other knowledge, and unproven. The consensus of the testimony presented at the subcommittee hearings does not support such action.

The testimony presented at the hearings supports the position that if there is determined to be a need for immediate legislation it should be directed solely toward extending the NIH guidelines to nonfederally funded research on recombinant DNA. I generally agree with that conclusion, although I am nevertheless concerned that we might initiate unnecessary and unreasonable restrictions on the conduct of basic scientific research. Even here the guidelines are already being applied voluntarily in the private sector. Certainly there should be only those minimal requirements necessary to ensure compliance with the guidelines.

Based on my experience in the scientific community and the general level of professional responsibility demonstrated by the scientists themselves, I cannot concur with the majority's conclusion that a system of voluntary compliance would be inadequate. I do believe that scientists must continue to insist on ethical compliance with the NIH guidelines and general principles of good research procedures.

There is a need to further examine alternatives to a harsh and unwieldy system of regulations for enforcing the guidelines. One example which appears promising is the use of patent withdrawal to enforce compliance with the guidelines. In his testimony before the subcommittee, David Newburger, assistant professor of law at Washington University, indicated that conditioning the grant of patents for discoveries resulting from research on recombinant DNA technology on a showing of compliance with the NIH guidelines would provide a substantial incentive for investigators to abide by the guidelines. Such a system would avoid the need for excessive regulatory and licensing requirements. The investigator would ultimately be held accountable for his adherence to the guidelines and a system of monitoring could be incorporated.

Uncertainties still exist with respect to the possible scope of such a system and whether it would reach all recombinant DNA research. Nevertheless, this is at least one option which deserves further examination before we set up a major regulatory structure.

ATTACHMENT A

The DNA Research Scare

(By Bernard D. Davis*)

Four years ago a group of molecular biologists publicly expressed grave concern over the potential dangers of research with recombinant DNA, a novel technique that allowed a small amount of DNA, the material of which genes are made, from any organism, to be incorporated into a bacterium. At their urging the National Institutes of Health issued an elaborate set of guidelines, forbidding the formation of certain kinds of recombinants and placing various restrictions on others. And last spring Congress was framing legislation carrying additional restrictions and harsh penalties.

But the NIH is now considering substantial relaxation of the guidelines, congressional committees are considering much milder legislation, and the need for any legislation is increasingly questioned. It is important to know why the dangers seem so much smaller today.

First, people for several years have been making recombinants in many laboratories, without a single resulting illness. It is clear that the predicted dangers remain entirely hypothetical.

Second, the recombinant technique is increasingly recognized as a tool of great versatility, comparable to the use of radioactively labeled molecules in studying the chemical processes in living systems. For example, recombinants make it possible to isolate human genes. Moreover, they also make it possible to study the action and the regulation of these genes in the thousandfold simpler background of a bacterial cell. And gene regulation—the selective turning on of some genes and turning off of others—is a crucial problem in modern biomedical science.

It is the key to the normal development of a fertilized egg into a human being, and also to the abnormal development of a cancer (a line of cells that have escaped from normal growth regulation). Other uses of recombinants, of more immediate medical and industrial importance, will include the manufacture of innumerable useful human products, such as insulin, other hormones, antibodies and antiviral agents. With such benefits in sight we will be paying an extravagant price if we perpetuate restrictions that are not justified by the hazards. Moreover, if this price involved only money, like the tens of millions of dollars wasted on lunar quarantine, it would be bad enough. But it also involves a greater, hidden cost: hindrance of research on diseases that are meanwhile taking human lives.

A DIFFERENT SCIENCE

Third, though the development of these novel recombinant organisms was created by specialists in molecular biology, the assessment of the possible hazard is a problem in quite a different area of science: infectious disease. Unfortunately, few professionals in this field were included in the early discussions, though they might have kept the scenarios within realistic bounds. The NIH finally assembled a world-

*Dr. Davis is Adele Lehman, professor of bacterial physiology at Harvard Medical School.

wide group of such experts last summer, and they agreed that the proposed recombinants could not be as dangerous as many known disease producing organisms, which are cultured in thousands of medical laboratories every day.

Fourth, the bacteria being used in this work are special, weakened strains, carefully developed to require nutrients that are not encountered in natural environments. Moreover, in the absence of these required compounds the cells not only fail to grow, they are rapidly suicidal: If they accidentally infected a laboratory worker they would all die within a few hours. Hence recombinants made with such strains could not conceivably spread. Moreover, experiments in the past year have shown that the chance of escape of the recombinant genes from these dying bacteria into healthy ones is infinitestimal.

"*Recombinant DNA is increasingly recognized as a tool of great versatility. . . . We will be paying an extravagant price if we perpetuate restrictions that aren't justified by the hazards.*"

Fifth, the present guidelines consider incorporation of the DNA of a virus into bacteria especially dangerous. But to cause disease, that DNA would have to be released from the host bacterium as naked DNA, which would then have to infect a human cell. This probability is also exceedingly low, for we know that the naked DNA of a virus is less infectious than the same DNA inside the viral coat, by as much as a million-fold. Recognizing these facts, European biologists are recommending great relaxation of the guidelines for virus-bacterial recombinants—much greater than that contemplated in this country. Hence excessive restrictions may cause this country to fall behind rapidly in this important area of medical research.

My sixth point concerns the class of recombinants containing human DNA. These have particularly broad promise for medical research; but they have been classified as particularly dangerous, because of fear that they might pick up and spread the genes of human viruses. But this fear is based on the additional assumption that these recombinants would be an entirely novel class of organisms, never encountered before in nature. With further discussion this assumption has become exceedingly unlikely. We know that bacteria can take up DNA (though infrequently); and since bacteria have been growing in the colons of our ancestors for millions of years, it is virtually certain that they have often taken up human DNA, released from dying cells of the surrounding intestinal wall. Accordingly, mankind must have long been exposed to recombinants of this kind.

Finally, the initial discussions not only neglected relevant principles of infectious disease, they also failed to take into account well-established evolutionary principles, which are essential for understanding the spread of any novel organisms.

Specifically, bacteria in great variety compete for survival and multiplication on various parts of our body, on plants and in the soil. The successful strains are those that are best adapted to a given location, and to be well-adapted they must have a well-balanced set of genes.

NATURAL SELECTION

This adaptation, and this balance, have been evolved over billions of years, by natural selection; it is a process that moves in small steps and that perpetuates only the tiniest fraction of all the genetic novelty

that appears. Hence splicing DNA from a distant source into a bacterium is not at all likely to produce a well-balanced, competitive set of genes, any more than inserting a random radio part would be likely to improve a watch.

With these developments, the initially very cautious attitude of the scientific community has shifted dramatically. The bluntest critique has come from James Watson (who triggered the development of molecular biology by his discovery, with Francis Crick, of the structure of DNA). Though he was one of those who first voiced caution, he now urges that we abandon the whole expensive bureaucracy of guidelines and release the wasted time and money for solving real health problems. It seems almost certain that Watson will prove right. But meanwhile it also seems clear that public anxiety, generated initially by scientists, cannot be reversed until the true nature of recombinant DNA research is widely understood.

The recombinant DNA story illustrates a broader problem: how to handle public policy issues that have a large technical content. If we wish to maximize beneficial research, without jeopardizing either public welfare or public confidence, we must find ways to work out more clearly the role of the community of experts in ascertaining the facts as objectively as possible, and the subsequent role of the broader public in making value judgments and policy decisions. For while the public has a right to know, it also has a right to be protected from false alarms. A useful model may be that of the medical profession, which often has to consider alternative diagnoses in a case but also exercises discretion in avoiding premature discussion of unproved possibilities that would unduly alarm the patient. Perhaps the scientific profession and the public are groping for a similar code.

ATTACHMENT B

The Nobelist vs. the Film Star

RESTRICTIONS ON DNA RESEARCH ATTACKED

(By J. D. Watson*)

Until the last year, I never thought much about my allegiances. My parents were for Roosevelt and against the spoilage of our land by senseless land speculators or industrial giants who put steel mills where there had been sand dunes and the prairie warbler had nested. People who went on bird trips or camped in the national forests and wanted to save Mineral King were the right sort, while those who owned big yachts or stripped the rolling fields of Ohio for coal were the bad guys whom we must get laws to stop. So it was natural to make out a modest check whenever Robert Redford or some equally fine fellow asked you to help him defend the environment and fight the polluters who would give us more cancer.

Now, however, I must confess that I didn't respond to Robert Redford's latest appeal. It is not that I am against him as a folk hero, but, though he must be unaware, he and I are, for practical purposes, real enemies. For some of the money he raises for the Environmental

*Watson, director of the Cold Spring Harbor Laboratory in New York state, won a 1962 Nobel Prize in medicine for his work on the structure of DNA.

Defense Fund is being used to try to stop the experiments we do with "recombinant DNA."

This test-tube-made genetic material now provides an incredibly powerful means to find out what human genes are like. And in so doing it will give us important new ways to think, say, about our immune systems, or how our blood cells are made or the nature of the genes that go out of control when cancer arises.

This being so, I most certainly am a Friend of DNA and want work with recombinant DNA to go as fast possible. In the old days, this impulse would generally be viewed as good for the earth. Now, however, there exist highly vocal groups who think I'm a danger to the world. The Friends of the Earth, the Sierra Club and the Natural Resources Defense Council, as well as the Environmental Defense Fund, all say that our experiments pose a realistic threat to our way of life and must be constrained by their new breed of environmental lawyers.

All this initially surprised me, since I had always regarded environmentalists as among our most intelligent public groups and thought that the original rub for work with recombinant DNA which had come out of the 1975 Asilomar Conference should more than reassure them. Particularly since I found those guidelines a terrible overkill and probably not at all necessary.

My fellow DNA workers wanted, however, to act more than clean and certainly to give the impression of being responsible citizens. So they suggested that we largely work with specifically enfeebled organisms that would not live well outside our test tubes. And when, after Asilomar, the matter was taken up by the National Institutes of Health, they in turn wanted to look like the perfect guardian of our health, and so the guidelines which we now have to live with became more than tough. In fact, they effectively blocked most of the better experiments that directly relate to cancer.

As a result, the DNA community is now very unhappy working under harsh rules we do not believe necessary and which waste vast sums of sorely needed research funds. We now want to relax greatly the guidelines we imposed upon ourselves.

Unfortunately, we find this task to be much more complicated than their original drafting. Our main problem is that in our original statements about recombinant DNA, we kept referring to "potential dangers." Instead we should have said "conjectural dangers," since there was, and still is, not a trace of evidence that any of the experiments pose a threat to those who do them, much less to the general public.

In being so linguistically sloppy, we gave a long awaited opening to two groups which were out to embarrass us. The first consists of disgruntled long-out-of-productive-science biochemists, who use any opportunity to say bad things about how the effects of modern science are carried out. The other is a tiny, though noisy, group of Boston-based academic leftists who fantasize that the rich will finally sub-

jugate the masses by giving them bad genes manufactured by recombinant DNA methodologies. This is a mad idea which I suspect they are too intelligent really to believe. It must be a tactical move in their zany campaign to convince the Boston poor to rise up against the elitist imperialism of MIT and Harvard.

We never expected, however, that we would be branded as polluters by the environmental movement. For until recombinant DNA came along, we always thought we were on their side.

After all, who wants to see our planet not fit for our children to inherit? When they went to court to block DDT or keep the skies of Monument Valley blue, we could only applaud. So why now are we on opposite sides? Can we have on blinders, and can our self interest as scientists not allow us to see how indifferent we are to the harm we may do? Might, in fact, the professional environmentalists present arguments that we just can't face up to?

I feel strongly this is not the case. Compared to almost any other object which starts with the letter D, DNA is very safe indeed. Far better to worry about daggers, or dynamite, or dogs, or dieldrin, or dioxin or drunken drivers than to draw up Rube Goldberg schemes on how our laboratory-made DNA will lead to the extinction of the human race.

The strains of viruses and cells we work with in the laboratory generally are not pathogenic for man, and all we know about infectious diseases makes it unlikely that the addition of a little foreign DNA will create any danger for those who work with recombinant DNA-bearing bacteria. Even if no special guidelines existed, and we only employed the standard microbiological practices of routine sterilization, we should have no reason to be concerned for our health. Equally important, we should not worry that our experiments will profoundly alter evolution by creating bizarre life forms unlike any seen before. DNA is frequently carried from one species to another by viruses, and the global evolutionary impact of our experiments must be negligible compared to naturally occurring DNA transfers.

If this is so, how can we explain the enthusiasm with which so many professional environmentalists wish to shut us down?

The answer, I fear, is that such groups thrive on bad news, and, the more the public worries about the environment, the more likely we are to keep providing them with the funds that they need to keep their organizations growing. So if they do not watch themselves, they will always opt for the worst possible scenario.

For the short term this may give them more recruits, but I worry about the long-term effect. No one will benefit if we perceive the credibility of our environmental movements to be no better than that of the most troglodytic of our industrial firms.

If what they say about DNA is nonsense, do we have any compelling reason to listen to them when they come out against pesticides that give us shiny apples or tell us that the waters of the Mississippi are likely to give us cancer? I would like someone to set me right on such matters, but whom to trust now is not that clear.

ATTACHMENT C

Research With Recombinant DNA—National Academy of Sciences

EPIDEMIOLOGICAL AND EVOLUTIONARY ASPECTS OF RESEARCH ON RECOMBINANT DNA

(By Bernard D. Davis)

* * * * * * *

Underlying Principles

NATURAL SELECTION

Evolutionary change arises ultimately from hereditary variation, but its direction is dominated by natural selection. It is dramatic for George Wald to state that research with recombinants is dangerous because "a living organism is forever"—but a more balanced statement would also note that only an infinitesimal fraction of the products of evolutionary experimentation survive, the rest being ruthlessly culled out by natural selection. In particular, within a species the process of sexual reproduction produces a virtually infinite variety of recombinants, among which the standard pattern of selection is a stabilizing (normalizing) one: excessive deviation from the norm make an organism less effective in the Darwinian competition. It is only when the environment is altered that certain deviants from the norm turn out to be better adapted to the new environment, and selection then becomes directional.

It should also be emphasized that all natural selection is for a balanced genome. A gene that increases or decreases a trait is selected for, not in a vacuum, but only if it is coadapted to the rest of the organism's total set of genes.

ATTACHMENT D

Interim Report of the Interagency Committee of Recombinant DNA Research and its Applications, March 13, 1977

SUGGESTED ELEMENTS FOR LEGISLATION

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IV. SUBCOMMITTEE REVIEW OF EXISTING LEGISLATION

At the November 23 meeting of the Interagency Committee, the Federal regulatory agencies also reported on their regulatory functions. Following that review, a special Subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of recombinant DNA research. All regulatory agencies were represented on the Subcommittee, assisted by attorneys from their offices of general counsel. (See Appendix II for the membership of the Subcommittee.) The Subcommittee held meetings on December 13, 1976, and on January 11 and February 8, 1977.

The Subcommittee was charged to determine whether existing legislative authority would permit the regulation of all recombinant DNA research in the United States (whether or not Federally funded) and would include at least the following regulatory requirements:

(1) review of such research by an institutional biohazards committee before it is undertaken,

(2) compliance with physical and biological containment standards and prohibitions in the NIH Guidelines,

(3) registration of such research with a national registry at the time the research is undertaken (subject to appropriate safeguards to protect proprietary interests), and

(4) enforcement of the above requirements through monitoring, inspection, and sanctions.

It was the conclusion of the Subcommittee that present law could permit imposition of some of the above requirements on much recombinant DNA laboratory research, but that no single legal authority or combination of authorities currently exists that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements. The complete Subcommittee analysis is included in Appendix III. The Subcommittee, in reaching this conclusion, reviewed the following laws that were deemed most deserving of detailed consideration:

(1) the Occupational Safety and Health Act of 1970 (Public Law 91-596),

(2) the Toxic Substances Control Act (Public Law 94-469),

(3) the Hazardous Materials Transportation Act (Public Law 93-633),

(4) Section 361 of the Public Health Service Act (42 U.S.C. Sec. 264).

The Occupational Safety and Health Act gives the Occupational Safety and Health Administration (OSHA) broad powers to require employers to provide a safe workplace for their employees. The term "employer" in the Act, however, is defined in such a way as to exclude States and their political subdivisions unless the OSHA standards are voluntarily adopted. Twenty-four States have adopted the standards, but twenty-six states are not subject to them. Further, the OSHA standards do not cover self-employed persons. For these reasons it was determined that OSHA at present could not regulate all recombinant DNA research.

The Environmental Protection Agency, under the Toxic Substances Control Act, is directed to control chemicals that may present an "unreasonable risk of injury to the health or the environment." The Subcommittee determined that the materials used in recombinant DNA research would appear to be covered in most cases by the Act's definition of "chemical substance." Section 5 of the Act, however, explicitly exempts registration of chemical substances used in small quantities for the purposes of scientific experimentation or analysis. This represents a most serious deficiency, as the registration of activities was thought to be an essential element of any regulatory effort. Also, in order to meet the specifications of the Act, recombinant DNA

research would have to be found to present "an unreasonable risk of injury to health or the environment."

The Hazardous Materials Transportation Act (HMTA) and Section 361 of the Public Health Service (PHS) Act give the Department of Transportation (DOT) and the Center for Disease Control (CDC), respectively, authority to regulate the shipment of hazardous materials in interstate commerce. Both the DOT and the CDC, in implementing these acts with respect to biological products, have essentially aimed at imposing labeling, packaging, and shipping requirements, and were found to be wanting for regulation of all recombinant DNA research.

The Environmental Defense Fund, in November 1976, petitioned the DHEW to regulate recombinant DNA research under Section 361 of the PHS Act. (The petition is included in Appendix IV.) The Subcommittee carefully reviewed this section, which is directed to organisms that are communicable and cause human disease. Thus, under this section, there would have to be a reasonable basis for concluding that the products of all recombinant DNA research may cause human disease and are communicable. Further, Section 361 does not apply to plants, animals, or the general environment. It was the conclusion of the Subcommittee that Section 361 lacked the requisiite authority to meet all of the requirements set for the regulation of this research.

The Subcommittee also considered the authority of the CDC to license and control the operation of clinical laboratories under Section 353 of the PHS Act, but this provision was not considered to be applicable to research laboratories.

Other authorities of EPA under the Clean Air Act, the Federal Water Pollution Control Act, and the Resource Conservation and Recovery Act of 1976 were considered briefly and thought only to apply, if at all, to isolated aspects of recombinant DNA research. The authorities of the Food and Drug Administration (FDA) were also reviewed, but it was concluded that recombinant DNA research has not yet reached the stage of commercial application that comes under the FDA's jurisdiction. The regulatory powers of the U.S. Department of Agriculture (USDA) were also reviewed and found applicable solely to nonhuman animals and plants.

In summary, the group concluded that no single legal authority, or combination of authorities, currently exists which would clearly reach all recombinant DNA research in a manner deemed necessary by the Committee. Although there is existing authority that might be broadly interpreted to cover most of the research at issue, it was generally agreed that regulatory actions taken on the basis of any such interpretation would probably be subject to legal challenge.

After completing an analysis of existing legislation, the Subcommittee on February 8, 1977, considered elements which might be included in legislation to regulate recombinant DNA research. The Subcommittee referred the analysis of existing legislation and elements for new legislation to the full Committee at a meeting held on February 25, 1977. The full Committee adopted the report of the Subcommittee on existing legislation and agreed that new legislation was required.

THE LIBRARY OF CONGRESS,
CONGRESSIONAL RESEARCH SERVICE,
Washington, D.C., May 12, 1978.

To: Hon. Harrison H. Schmitt.
From: American Law Division.
Subject: Questions concerning the applicability of section 361 of the Public Health Service Act to recombinant DNA research.

The following memorandum has been prepared in response to your several questions regarding HEW's regulatory authority under Section 361 of the Public Health Service Act (42 U.S.C. § 264). Specifically, you have requested our opinion as to the regulatory scope of Section 361 andits applicability topublic and private recombinant DNA research.

Initially, we must agree, based on our own extensive research, with the Federal Interagency Committee on Recombinant DNA Research that "no single legal authority or combination of authorities currently exist that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements." In a paper we prepared last December, we came to the same conclusion:

> In brief, comprehensive regulation of the products resulting from recombinant DNA research techniques does not appear feasible under current laws. At best, regulation will be piecemeal and dependent on the uses for which those products are intended. Regulation will be dispersed throughout several federal agencies, where the research activities involved come under the respective department or agency mandate and it will be limited by the purposes enumerated in the appropriate authorizing legislation.

Several of your questions deal with Section 361 (42 U.S.C. § 264). While it can certainly be argued that section 361 does authorize the Secretary of HEW to promulgate regulations to protect the public from the introduction or spread of any suspect communicable disease, thus authorizing the regulation of recombinant DNA research, it is a highly disputed interpretation of the section. The section, on its face, refers to the prevention of the spread, etc. of communicable diseases. Admittedly the language of Section 361(a) is rather broad. However, specific statutory limitations in subsections (b), (c) and (d) to "diseases as may be specified" and to the control of interstate and foreign travel of infected persons, suggest that control of private intrastate research to assure protection of the public and environment from unknown dangers and unspecified diseases may well be outside the scope of the section. It can hardly be argued that Congress intended, when the original quarantine law was enacted,[1] or superceded, that this regulatory authority extended to research which is just now becoming feasible. While there is no doubt that Congress intended the appropriate federal authorities to have broad and flexible powers (i.e. "the use of conventional public-health enforcement methods")[2] to prevent the spread of dangerous and destructive disease, it surely did not mean that scientific research was to be pervasively regulated.

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[1] Originally enacted in 1879 (Act of Mar. 3, 1879), superseded in 1893 (27 Stat. 449), and in 1944 (58 Stat. 703.).
[2] This language is from the House report accompanying the 1944 amendments.

There are few decisions of the courts in which these public health provisions have been construed. But those cases that have considered the scope of section 361 do not provide convincing authority for the belief that the Secretary's powers under that section are as broad as they must be to accomplish pervasive regulation of recombinant DNA research. The most recent case to construe section 361 was decided last year by the federal district court in the eastern district of Louisiana. *Louisiana* v. *Mathews*, 427 F.Supp. 174 (1977). The Secretary of HEW had banned the interstate and intrastate sale of all small turtles because of the danger that the turtles were or *might be* infected with two known communicable diseases. In that case, the court reasoned because the chances of contamination or re-contamination of turtles were so high (54 percent or greater), that "a total ban is permissible as necessary to prevent the spead of communicable disease." The alternative, the court noted, was to adopt a "patently unreasonable" and "onerous testing scheme." While an intrastate ban was deemed necessary, and the court sanctioned regulation to prevent the possibility of spread, etc. of disease, it is significant that well-known and widespread communicable disease already specified in the federal regulations were involved. Thus, the Secretary's regulatory authority will, in some cases, extend to intrastate regulation of potential disease, but the case does not support the conclusion that this is true in all circumstances, particularly those involving unspecified and as yet non-existent "diseases." We found no case supportive of the position that hypothetical dangers and diseases are within the scope of section 361.

On the other hand, presented with a case involving grave danger and the possible spread of recombinant DNA generated disease, the courts may choose to give section 361 and even more expansive interpretation that was applied in *Louisiana* v. *Mathews*. It should be considered however, that the courts have not yet dealt with this and litigation would inevitably result from extension of section 361 to recombinant DNA research. We have reviewed the letter of January 6, 1978 from Peter Barton Hutt to Gilbero S. Omenn and we recognize that his argument is persuasive. But we cannot, with assurance conclude that the Secretary's regulatory authority under section 361 is as broad as Mr. Hutt suggests. In the event that new legislation to provide authority for DNA regulation is deemed inadvisable at this time, we do agree that the Public Health Service Act may currently be the most effective means to regulate the conduct of recombinant DNA research.

Additionally you have asked for legal precedent supportive of the use of section 361 to regulate nonbacterial or nonviral research. The Drinking Water Standards, set out at 42 C.F.R. § 72.20, define pollution to mean the presence of "any foreign substance" including "organic, inorganic, radiological, or biological" products that may "constitute a hazard or impair the usefulness of the water." Currently however, these standards are the only ones promulgated under the Public Health Service Act which extend beyond bacterial, fungal, or viral, rickettsial and chlamydial etiologic agents. See, 42 C.F.R. § 72.25 (a) (c). We are aware of no court case that has dealt with the further extension of these regulations to agents other than virable organisms and their toxins.

As to the Secretary's preemptive authority under section 361, "the purpose of Congress is the ultimate touchstone." *Retail Clerks* v. *Schermerhorn*, 375 U.S. 96, 103 (1963). An early Supreme Court case which upheld a state's quarantine laws (alleged to be in conflict with federal law), stated that "quarantine laws belong to that class of state legislation which is valid until displaced by Congress, and that such legislation has been expressly recognized by the laws of the United States almost from the beginning of government." *Compagnie Francaise* v. *Louisiana Board of Health*, 186 U.S. 380, 389 (1902); *Louisiana* v. *Texas*, 176 U.S. 1, 21 (1899). In enacting the federal quarantine laws (subsequently superseded by section 361), the Congress apparently did not express a specific intent to preempt state laws on the subject. The Supreme Court has stated that "we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Rice* v. *Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947): *Jones* v. *Rath Packing Co.*, 430 U.S. 519, 525 (1977). The most recent Supreme Court decision concerning federal preemptive capacity set out the general principles:

> Often Congress does not clearly state in its legislation whether it intends to pre-empt state laws: and in such instances, the courts normally sustain local regulation on the same subject matter unless it conflicts with federal law or would frustrate the federal scheme, or unless the courts discern from the totality of the circumstances that Congress sought to occupy the field to the exclusion of the States. *Malone* v. *White Motor Co.*, No. 76–1184 (April 3, 1978), slip opinion at 6.

Absent expressed congressional intent, it is probable that Section 361 does not give the Secretary of HEW authority to preempt state laws. Additional legislation is needed to accomplish that purpose.

In response to your additional questions regarding the Secretary's authority to license and inspect facilities, to extend guidelines to non-federally funded research, etc., we can not provide clear cut answers. Needless to say, all the powers you mention in your letter would significantly expand HEW's role in public health regulation from what it has been. Under Section 361(a) the Secretary has the power "to make and enforce such regulations as in his judgment are necessary" to fulfill the section's purpose. But again, for the reasons we have discussed throughout this paper, we can not say that all DNA activity will be subject to the Secretary's control. For the research that is, little question exists that the Secretary has the power to inspect and license facilities if it is in fact necessary and the constitutional and statutory rights of involved individuals are respected. As for intrastate regulation absent federal funding, there must be a clear relationship of the intrastate activity to some aspect of interstate commerce to justify federal regulation. If that nexus is established then the intrastate activity is subject to federal regulation as is necessary to accomplish the statutory purpose. See, *Louisiana* v. *Mathews*. Again, however, non-federally funded, wholly intrastate activity bearing no relationship to interstate commerce is not within the regulatory ambit of section 361.

23-890—78——6

Violations of section 361 are presently punishable under section 368(a) of the Act which provides that any person who violates section 361, etc., "shall be punished by a fine of not more than $1,000 or by imprisonment for not more than one year, or both." Presently, injunctive relief for violations of section 361 is not specifically authorized under the Public Health Service Act.

Because of the constraints of time we are not able to provide a detailed comparison of the Secretary's authority under Senate Amendment 1713 and H.R. 11192 with the potential scope of his authority under section 361. It is obvious though, that under the pending legislation the Secretary's authority is subject to less dispute and clearly is more encompassing than it would be under section 361. The procedures for inspections are set out by Congress in the pending legislation. Should section 361 be used for regulation then HEW must develop its own procedures. Preemption will be accomplished under the pending legislation whereas preemptive capacity under section 361 is unlikely to exist. Injunctive authority is also clearly provided for in the pending legislation. Furthermore, the provision in the pending legislation for a study of DNA research and its applications could be useful in providing guidelines for future regulation of such a new and unprecedented area.

We hope that this information will be helpful. If you need additional information or analysis please feel free to call on us.

DONNA C. PARRATT,
Legislative Attorney.

THE LIBRARY OF CONGRESS,
CONGRESSIONAL RESEARCH SERVICE,
Washington, D.C., May 18, 1978.

To: Hon. Harrison H. Schmitt (Attn: Bill Gibb).
From: American Law Division.
Subject: Appraisal of correspondence concerning scope of authority Under the Public Health Service Act.

As you requested as a follow up to our memorandum of May 12 regarding the use of section 361 of the Public Health Service Act to regulate recombinant DNA research, we have more carefully reviewed Mr. Peter Barton Hutt's letter of January 6 to Dr. Gilbert S. Omenn, We expressed the belief in our previous memorandum that although Mr. Hutt's arguments appear to have some force, we could not reach the very broad and general conclusions he did based on our interpretations of existing statutory and case law. You have asked us to elaborate on that position by addressing several particular conclusions expressed by Mr. Hutt in his letter.

First, you have asked us to analyze Mr. Hutt's position about the application of Section 361 to intrastate commerce. Mr. Hutt states on page three that this issue has been "definitively resolved by [*State of Louisiana* v. *Mathews*] upholding the legality of an FDA regulation banning all small pet turtles from both intrastate and interstate commerce under the sole authority of Section 361." In the last paragraph on page four, he further states that the court in *Louisiana* "ruled that section 361 permits FDA to control intrastate as well as interstate activity."

However, *Louisiana* did not hold that section 361 permits FDA to control intrastate activity in *all* circumstances. The court clearly explained that the intrastate ban was justified only because it was necessary to prevent the interstate spread of disease. As the court explained, the FDA regulation was due to the "particular facts and circumstances underlying the ban on turtles" which are not present in all cases.[1]

With reference to DNA research, there is no evidence to support the position that intrastate regulation is necessary to prevent the interstate spread of communicable disease. Any hazards arising from recombinant DNA research are at this point in time purely speculative. Mr. J. D. Watson, an eminent authority on DNA, recently wrote:

> [I]n our original statements about recombinant DNA, we kept referring to "potential dangers." Instead, we should have said "conjectural dangers," since there was, and still is, not a trace of evidence that any of the experiments pose a threat to those who do them, much less to the general public. . . .
>
> The strains of viruses and cells we work with in the laboratory generally are not pathogenic for men, and all we know about infectious diseases makes it unlikely that the addition of a little foreign DNA will create any danger for those who work with recombinant DNA-bearing bacteria. Even if no special guidelines existed, and we only employed standard microbiological practices of routine sterilization, we should have no reason to be concerned for our health.[2]

Therefore, while we agree with Mr. Hutt that intrastate commerce certainly may be regulated to prevent the spread of communicable disease, we cannot agree that all DNA research poses such a substantial threat of disease that all intrastate DNA activity can be reached under the Public Health Service Act. Mr. Hutt's position is based on an assumption that the "very nature of the controversy itself is sufficient . . . to establish the potential for harm that is required under Section 361. If that potential were agreed not to exist, the entire issue of regulatory control over this research would never have been raised in the first place." Needless to say, his position is not universally held.

Other considerations as well suggest that section 361 might not be interpreted to apply, across the board, to all recombinant DNA research. We briefly commend in our previous memorandum that the legislative intent behind the Public Health Service Act can hardly be said to comprehend recombinant DNA research even though the regulatory authority intended under the Act is broad. Because of the unique nature of recombinant DNA research, arguments can be made that absent express legislative intent the Public Health Service Act should not be utilized to regulate DNA work. It has been argued that recombinant DNA research, especially when conducted in an academic setting, involves First Amendment freedoms of speech. This has been urged by several constitutional law scholars as well as concerned and involved scientists. The nation's highest court has expressed in sev-

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[1] See, e.g. 42 C.F.R. 72.21 ; 72.22.
[2] *The Washington Post*, Sunday, May 14, 1978, p. D–2.

eral cases a strong commitment to the principles of academic and intellectual inquiry and a presumption against governmental interference. In testimony last May before the House Subcommittee on Science, Research and Technology, Professor Thomas I. Emerson of Yale Law School expressed his belief that at least some aspects of recombinant DNA work must be characterized as deserving of First Amendment protections:

> The first question . . . is whether the conduct involved in DNA research constitutes "expression" or "action." It seems to me that the development or exposition of theoretical ideas about DNA and other genetic materials and processes is clearly expression. Such conduct involves the search for truth in its primal form. The fact that the researcher works physically with complicated equipment does not deprive the conduct of its character as expression. In similar fashion a telescope is used to study the stars, an accelerator to study nuclear particles, a public address system to carry on a public meeting, and a xerox machine to make copies for distribution.
>
> The more difficult question is the classification of experimentation. Experimentation is a vital feature on the development of new information, ideas, and theories. This is particularly so in the physical sciences. One must conclude that it is often an integral part of scientific research, that is, a part of the system of freedom of expression. Analogous conduct is the marching in a demonstration, the publication of a newspaper, and the organization of a political party. Although all such conduct involves more than sheer thinking or verbalization, nevertheless it is an essential feature of a system of free expression.
>
> On the other hand, at some point experimentation clearly moves into the realm of action. Just as political assassination has an element of expression but is basically action, so an experiment to test a theory of nuclear energy which might blow up a city, or contaminate the atmosphere of the whole world, is also predominantly action. The line has to be drawn on the basis of all the facts in a particular case and —in light of the proper function of a system of freedom of expression in a democratic society.
>
> On the basis of present information available to me it is difficult to state more specifically what forms of experimentation should be classified as expression, and what as action. It does seem clear, however, that experiments which pose a serious threat to the physical health or safety of a community, must be classified as action. Such conduct is analogous to the use of violence against persons or property in a demonstration, or the throwing of rocks through the windows of the White House. The physical element of the conduct is the paramount concern, and the conduct therefore falls into the realm of action rather than the expression of ideas.
>
> On this analysis, the broad search for information about DNA, the formulation of hypotheses, the exposition and discussion of theories and methods would constitute expression,

> and be fully protected under the First Amendment. Thus the government could not prohibit, regulate or discourage in any way DNA research on the ground that mankind ought not to be pursuing ideas about ways to develop new forms of life. On the other hand experiments that presented a *substantial and serious danger* to the physical health and safety of the surrounding population could be subject to regulation without infringing the guarantees of the First Amendment. Only the requirements of due process, equal protection and other constitutional provisions would be applicable to such regulation. [Emphasis added.]

We are thus confronted with the additional problem that the proposed regulation may result in stifling the freedom of scientific inquiry. Using the framework developed by a noted constitutional law scholar at Harvard, Laurence H. Tribe, government regulation of DNA research might be described as being "aimed at noncommunicative impact but nonetheless having adverse effects on communicative opportunity." [3] Government action in a case of this sort requires the balancing of competing interests. According to Mr. Tribe, "regulatory choices aimed at harm not caused by ideas or information as such are acceptable so long as they do not *unduly* constrict the flow of information and ideas." [4] Presented with this difficulty should DNA research be characterized as having constitutional implications, the courts may be unwilling to uphold the use of section 361 for a purpose not clearly intended when the law was enacted.

Although there is little legal authority related to this problem, a recent case involving the Federal Communication Commission's regulatory authority over cable television suggests that agency jurisdiction, even when its mandate is broad, is not without limits. *Home Box Office, Inc.*, v. *FCC*., 567 F2d 9 (C.A.D.C. 1977). In that case, the court was faced with F.C.C. regulation of cable television under the Communications Act of 1934. No provision in that Act authorized such regulation. The court cited Supreme Court precdent sanctioning the regulation of cable television "but only where the ends to be achieved were 'long established' in the field of broadcast television or were 'congressionally approved'" *Id.*, at 13 (citations omitted). This concern was of particular importance because of the First Amendment implications involved in regulation of the media. In an even more recent case, the Eighth Circuit also struck down F.C.C. regulation of cable television. *Midwest Video Corp.* v. *F.C.C.*, 571 F2d 1025 (8th Cir., 1978). The court expressed grave concern with governmental intrusion in areas affecting the exercise of Constitutional rights:

> Though we find it unnecessary to resolve the serious constitutional issues raised, we do hold that where, as here, potential incursions into sensitive constitutional rights are involved, *careful scrutiny is required in delineating the scope of authority Congress intended the agency to exercise. Id.*, at 1052 [Emphasis added.]

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[3] *American Constitutional Law*, by Laurence H. Tribe (Mineola, New York: 1978), p. 580.
[4] *Id.*, at 581–582.

In *Home Box Office*, the court emphasized that the F.C.C.'s authority goes "no farther than to allow the Commission to regulate to achieve 'long established' goals or to protect its 'ultimate purposes.'" *Id.*, at 28. In striking down some of the regulations, the court relied in part on a Supreme Court case involving a Civil Service Regulation barring resident aliens from employment in the federal competitive civil service. *Hampton* v. *Mow Sun Wong*, 426 U.S. 88 (1976).

In *Mow Sun Wong*, the Supreme Court emphasized that it was dealing with "a federal rule having nationwide impact." *Id.*, at 100. The Court also acknowledged that federal power over aliens (like the interstate commerce power) is plenary. *Id.*, at 101. But, the Court was concerned that at stake were liberty rights of these lawfully admitted individuals and that the decision to bar them from federal employment had been made at an agency level, rather than by Congress. Because constitutional interests were involved, despite the fact that the federal power is so plenary, the Court held that the Civil Service Commission regulation was unconstitutional. "The decision to impose that deprivation of an important liberty," the Court wrote, "must be made at a comparable level of government or, if it is to be permitted to be made by the Civil Service Commission, that it be justified by reasons which are properly the concern of that agency." *Id.*, at 116. The Court found that "the Commission performs a limited and specific function"—"promotion of an efficient federal service." *Id.*, at 114.

A comparison might be drawn between these cases and the suggested use of the Public Health Service Act to regulate recombinant DNA research. The purpose, as stated, of the Public Health Service Act is to prevent the spread of communicable disease. If constitutional rights are present, as many have argued, and the dangers from the research at this point are remote and purely speculative, then it may be argued that *Congress* should, if it finds it necessary, enact specific legislation with the clear purpose of protecting the environment from strains of viruses and cells that many scientists claim "generally are not pathogenic to man." See, infra, p. 2.

We are not raising these points to say that section 361 can not or even should not be used to regulate DNA work, but, we are saying that given the complexity of the problem, use of section 361 is sure to generate time-consuming and costly litigation, the outcome of which is unpredictable. The nature of the proposed regulatory scheme is such that we cannot conclude that the scope of section 361 is, without doubt, sufficiently broad to support pervasive regulation of *all* DNA research.

You have also asked for clarification of Mr. Hutt's statement on page seven concerning judicial review of administrative action. He states that HEW has "broad discretion . . . to determine when the scientific evidence warrants reliance on Section 361 to prevent the possibility of communicable disease. Absent evidence that the HEW decision is *wholly irrational*, it is highly likely that the courts would uphold this exercise of discretion." [Emphasis added.] The applicable standard for judicial review of administrative agency action is found in the Administration Procedure Act. 5 U.S.C. 706. The scope of review is not whether agency action is "wholly irrational," but rather whether the agency action is: "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law; contrary to constitu-

tional right, power, privilege, or immunity; in excess of statutory jurisdiction, authority, or limitations, or short of statutory right; or without observance of procedure required by law." See, e.g., *Louisiana* v. *Mathews* for an example of application of this standard. Clearly these standards are much different from a test to determine whether agency action is "wholly irrational."

Finally, you have asked for legal precedent which supports the following statement from page eight of Mr. Hutt's letter: "All that is needed to support regulations under this provision is either apprehension or uncertainty about the possibility of potential harm, the lack of adequate information showing that the harm cannot occur, and the possibility that the harm would be serious (e.g., irreversible) if did occur." That standard is not found in the statute or in the regulations promulgated under it. Nor has any court, to our knowledge, applied such broad language. Certainly more is needed than merely "the lack of adequate information showing that the harm cannot occur" to justify intrusive government regulation.

Again, we hope this is responsive to the questions you have asked. If we can be of further assistance, please feel free to call on us.

DONNA C. PARRATT,
Legislative Attorney.

ATTACHMENT E

THE UNDER SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., May 4, 1978.

Hon. HARRISON A. WILLIAMS, Jr.,
Chairman, Committee on Human Resources,
U.S. Senate, Washington, D.C.

DEAR PETE: I understand the Human Resources Committee will discuss possible action regarding DNA legislation in a markup session on Thursday, May 4.

I am enclosing a letter from the Secretary to Senator Stevenson and Dr. Fredrickson's testimony before the House Science and Technology Committee which express our strong support for passage of legislation similar to H.R. 11192. We do not believe Section 361 represents appropriate authority to achieve uniform regulation of DNA activities. In view of imminent House passage of H.R. 11192, we would urge the Human Resources Committee to consider passage of comparable legislation.

Sincerely yours,

HALE CHAMPION,
Under Secretary.

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,

Washington, D.C., February 27, 1978.

Hon. ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space, Committee on Commerce, Science, and Transportation, U.S. Senate, Washington, D.C.

DEAR ADLAI: This is in response to your letter of November 30, 1977, regarding our current and proposed authorities related to the control

of recombinant DNA research and related activities. Responses to questions directed to the Food and Drug Administration are also included in this letter.

1. Section 361 of the Public Health Service Act

Section 361 authorizes the Secretary of HEW to take action to prevent the introduction, transmission, and spread of communicable diseases from foreign countries and from State to State. The Interagency Committee on Recombinant DNA Research examined existing laws, including section 361, to determine if they provided adequate authority to regulate all recombinant DNA activities. The Committee concluded that new and specific legislation was needed.

The Committee's report (a copy of which is enclosed) released March 15, 1977, contains the following conclusion concerning section 361:

"Section 361 could perhaps be interpreted more broadly to serve as legal support for more comprehensive regulation. However, in order to do so there would presumably have to be a reasonable basis for concluding that the products of all recombinant DNA research cause or may cause human disease. Such a conclusion would undoubtedly be tenuous at best, and it is unlikely that resulting requirements could be effectively imposed and enforced."

On November 11, 1976, the Environmental Defense Fund and the Natural Resources Defense Council filed a petition with the Secretary of HEW asking him to impose regulations on all recombinant DNA activities, citing section 361 as authority (see Appendix IV of the Interagency Report). As explained in their petition (see pp. 57–59), they argued that the definition of communicable disease under section 361 can be read to include all recombinant DNA activities.

The Department has used section 361 to regulate a number of products which affect human health, including shellfish, pet turtles, primates, milk, drinking water, and human blood. Our Office of the General Counsel, however, believes it is preferable for a regulatory effort of the magnitude required to oversee all recombinant DNA activities, whether or not known to affect human health, to be based on the explicit support of the Congress as well as that of the Administration, particularly in light of the active interest the Congress has shown in this area. The consensus needed for this type of program is not best established by applying a general provision of law to this specific situation.

2. Other HEW Authorities

The Food and Drug Administration (FDA) is responsible for assuring that human drugs, biologics, medical devices, foods, cosmetics, and animal drugs, are safe, effective, and are produced in conformity with good manufacturing practices. For all new drugs, new animal drugs, biologics, food additives and color additives, and medical devices, the sponsor or manufacturer has the burden of demonstrating the safety and efficacy of product proposed for marketing. The Federal Food, Drug, and Cosmetic Act requires manufacturers of such products to submit safety and efficacy data supporting their petitions to FDA for review and approval before the product is introduced into interstate commerce.

The FDA has responsibility to safeguard the public from all potential hazards that may result from the development of products that are

subject to the Agency's jurisdiction. This authority would extend to research on regulated products where recombinant DNA is involved. The Agency could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the National Institutes of Health (NIH) Guidelines on recombinant DNA. For example, certification could be required for biologics, requests for certification could be required in petitions, such as new drug applications, license applications for biologics, requests for certification of antibiotics, and notices of claimed investigational exemption of a new drug. In addition, FDA under its investigational authorities may inspect firms making such certification to assure that they do, in fact, comply with the NIH guidelines. The Agency does have a number of regulatory sanctions it could bring to bear on any firm not in compliance with the Guidelines. These range from a denial of the petition to court actions.

3. Preemption of Federal Statutes

The Interagency Committee recommended in its report that HEW be the locus for the regulation of recombinant DNA activities. This is a sound suggestion, since a lead agency is essential to avoid duplication and to ensure uniform implementation of any DNA legislation. The Administration's bill provides that the proposed authority would "not affect the authority of any Federal agency to regulate under any other Act activities involving recombinant DNA." However, because the primary basis for controlling recombinant DNA activities is based on the potential threat to public health, other agencies should consult with HEW when those regulatory activities involve DNA.

The Department continues to support legislation to promote regulation of recombinant DNA activities as submitted to the Congress by this Department. We appreciate the contribution you and your Subcommittee have made to rational decisionmaking in this sensitive policy area. If we may assist in any way in your continuing work in this area please call on us.

Sincerely,

JOSEPH A. CALIFANO, Jr.

ROUND ANOTHER HELIX IN THE LEGISLATIVE HELTER-SKELTER[1]

The latest twist in Congress' current attempts to draw up a recombinant DNA bill is a move which means that there may be no bill at all. According to his staff aides, Senator Edward Kennedy has now decided that no bill is necessary, a sentiment which is the polar opposite of his position last year but identical to that of the year before.

No one is predicting where Kennedy, or at least his staff aides, will be next week; but on present showing there may perhaps—but not definitely—be no Senate action this session and therefore no legislation at all.

The prospect is welcomed by scientists who oppose government regulation of research in principle, but is causing concern to those who hoped through legislation to preempt state and local authorities from

[1] *Science* magazine vol. 200, May 19, 1978.

writing rules more restrictive than the existing National Institutes of Health guidelines.

Meanwhile at a meeting last month the NIH committee that wrote the guidelines approved several important changes, including a proposal to delegate authority for initial approval of recombinant DNA experiments from the NIH to institutional committees. Experiments would still be reviewed by NIH, but could begin as soon as local approval was obtained, cutting bureaucratic delay by some 3 to 4 months. The NIH committee also proposed reducing experiments with viruses to much lower containment levels.

If Congress fails to pass a bill, the Administration will then have to choose between continuing the present approach of voluntary adherence to the NIH guidelines, and invoking existing legal authority to give the guidelines the force of legislation. Each choice has its own advantages and difficulties.

It is far too early, however, to rule out the possibility of a Senate bill. The latest move by Kennedy's staff aides is not as inconsistent as it may seem. Although it is ascribed by aides to a change in Kennedy's perception of the hazards over the last 10 months, Kennedy has always seemed to be less interested in the possible risks of the research than in the principle of allowing the public and local authorities a voice in decisions about research. The bill pending in the House, which also has strong general support from certain senators, would preempt that role. Probably not having the votes to defeat preemption in the Senate, Kennedy's staff may hope to obtain the same end by inaction.

Those who favor preemption, such as the NIH and the American Society of Microbiologists, may therefore press for a Senate bill to be passed. Other interested parties, such as Senator Adlai Stevenson, may also favor a Senate bill if the Administration declines to use existing powers.

Where matters now stand is that, at a meeting of staff aides of the Senate human resources committee on 1 May, it was decided that Kennedy would write to HEW Secretary Joseph Califano to the effect that legislation seemed unnecessary if the Administration were prepared to use already existing powers.

Califano's response is hard to predict because the thought of no legislation at all is too new for people to have decided what they would like to do instead. Nor is the Administration all of one mind. The NIH favors strong preemption, believing that a law without preemption would be the worst of both worlds. For this, among other reasons, the agency is lukewarm toward invoking existing authorities, such as Section 361 of the Public Health Service Act, which gives the Secretary of HEW sweeping powers to control communicable diseases but not to preempt state governments.

Other parts of the Administration, however, such as the White House staff, are not so hot for preemption and could live with Section 361. As the result of an internal compromise, NIH director Donald Frederickson recently testified in support of a weaker form of preemption than that stipulated in the House bill.

"It is our judgment that many aspects we desire could be achieved under Section 361," says Gilbert Omenn, a staff member of the President's science adviser's office. But he also notes that voluntary compliance has worked well.

Kennedy's letter to Califano will probably ask, among other things, if Section 361 is an appropriate vehicle for regulating recombinant DNA. "Our response will be that simple legislation is required, and that 361 is not an appropriate statute," says an NIH official. In the NIH view, the section does not explicitly offer preemption (although some legal opinion holds that it would do so in practice), use of the statute might imply that recombinant DNA could give rise to communciable disease, and in any case Congress should carefully frame a special new law if it wishes to take the step of regulating biological research.

The problem of how to govern recombinant DNA research is as far from certain solution as ever, but the present range of likely outcomes is generally much less restrictive than those prevailing last year.—N.W.

ATTACHMENT F

U.S. SENATE,
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION,
Washington, D.C., May 4, 1978.

DEAR MR. SECRETARY: As you are undoubtedly aware, Congress is currently considering legislation which would regulate recombinant DNA research and its applications. The use of recombinant techniques to modify the fundamental genetic material offers great promise for all of mankind through improved understanding of biological processes, and varied applications in such fields as medicine, production of enzymes for industry, and agriculture.

Nevertheless, as with any new field of scientific research, it is impossible at this stage to say with absolute certainty that there is no hazard attendant to such research. To date, there have been no illnesses or other harm associated with recombinant DNA research. There have been recombinant processes occurring in nature since life began, and nature has built-in defenses against aberrant DNA strains. However, we cannot ignore the theoretical risks and the necessity to protect the health and safety of the public and the environment until further evidence is accumulated.

The implications for all of science and technology from the regulation of scientific research dictate that we move cautiously and fully explore all of the alternatives and ramifications before embarking on a course of regulation. The Senate Science, Technology, and Space Subcommittee, of which I am the ranking member, held three days of hearings during November, 1977, to consider the major policy issues associated with recombinant DNA research. The general thrust of the testimony from the more than 20 witnesses was that if there is determined to be a need for legislation it should be directed toward extending the National Institutes of Health (NIH) guidelines to non-Federal funded research on recombinant DNA. I generally agree with that conclusion, although I am concerned that we might initiate unnecessary and unreasonable restrictions on the conduct of basic scientific research.

Both the House and the Senate have bills pending which would extend the NIH guidelines to the private sector and assign responsibility

to the Secretary of HEW to promulgate administrative and enforcement regulations. Despite attempts to accommodate all interested parties, the proposed legislation has been criticized by both environmental groups and members of the scientific community. As the debate continues over the most appropriate means of extending the NIH guidelines, one must consider all options which might be effective.

In that regard, considerable attention has been focused recently on the application of Section 361 of the Public Health Service Act (42 U.S.C. § 264) to recombinant DNA research in lieu of legislation. Under this Section the Secretary of HEW is authorized to "make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases . . .". It has been suggested that Section 361 provides adequate statutory authority to extend the NIH guidelines to the private sector and to promulgate such regulations as are deemed necessary to ensure compliance with the guidelines. However, uncertainty remains as to the scope of coverage of Section 361 and its applicability to situations where DNA research represents a potential threat to plants, animals, and the environment. Until we fully understand the implications of relying on Section 361, it would be imprudent to recommend its application to recombinant DNA research.

In order to assist the Congress in its deliberations over this most difficult issue, I would appreciate your response to the following:

—What is your analysis of the provisions of the two principal bills (H.R. 11192 and Senator Kennedy's Amendment No. 1713 to S. 1217) pending before Congress which would regulate recombinant DNA research?

—If Senate Amendment No. 1713 as presently drafted were enacted into law, what specific steps would you take to implement the requirements of that legislation?

—The Federal Interagency Committee on Recombinant DNA Research concluded that "no single legal authority or combination of authorities currently exist that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements." Do you agree with that conclusion?

—Do you feel Section 361 contains adequate statutory authority to implement enforcement of the NIH guidelines to the private sector?

—What problems, if any, do you see arising from the use of Section 361 to regulate recombinant DNA research?

—If directed to regulate recombinant DNA research pursuant to Section 361, what specific regulatory action would you take to ensure private sector compliance with the guidelines?

—What legal precedent supports the application of Section 361 to recombinant DNA research or other forms of nonbacterial or nonviral research?

—What legal precedent would indicate that Section 361 is not appropriate for regulation of recombinant DNA research?

—What action, if any, do you plan to take if it becomes clear that Congress will not pass legislation this session extending the NIH guidelines to the private sector?

—Although the authority of the Secretary to regulate recombinant DNA activities is outlined in both the House and Senate bills,

I am unclear as to the specific regulatory authority of the Secretary under Section 361. Please provide a comprehensive analysis of the Secretary's total authority under Section 361 to regulate recombinant DNA research and related activities, including but not limited to the following items:

a. extension of the NIH guidelines to non-Federally funded research;

b. authority to license facilities;

c. authority to inspect facilities;

d. authority to promulgate regulations for administration and enforcement of the guidelines;

e. sanctioning authority with respect to civil penalties, injunctive authority, and criminal penalties;

f. role of local biohazard committees.

—Please compare the authority of the Secretary regarding recombinant DNA research and related activities under Section 361 with the authority of the Secretary under Senate Amendment 1713 and H.R. 11192.

—Does the Secretary have authority under Section 361 to preempt State and local actions concerning recombinant DNA research and related activities?

To assure that the Senate is informed on these very important issues prior to consideration of the pending legislation, I would request that you respond to this letter by May 13, 1978. Thank you for your continued cooperation.

Very truly yours,

HARRISON H. SCHMITT,
U.S. Senator.

ATTACHMENT G

EXECUTIVE OFFICE OF THE PRESIDENT,
OFFICE OF SCIENCE AND TECHNOLOGY POLICY.
Washington, D.C., May 18, 1978.

Hon. HARRISON H. SCHMITT,
U.S. Senate,
Washington, D.C.

DEAR JACK: Thank you for your letter of May 8, with questions about current legislation which would regulate recombinant DNA research and its applications.

Many of the issues you have raised, of course, we have discussed in previous correspondence and during the hearings on November 8 and February 10. As Gil Omenn testified to the House Science and Technology Subcommittee on April 11, we do support the passage of H.R. 11192. A copy of that testimony is attached.

Responses to your specific questions follow:

1. Analysis of the key provisions of the H.R. 11192 and S1713. The Administration prefers H.R. 11192 for the reasons stated in the Omenn testimony of April 11. The key provisions are the authority to waive regulation of much work which is judged to bear minimal risk; the authority to carry out potentially "high-risk" experiments in order to assess actual risks; and the mechanism for uniform national standards and regulations, with a means for local appeal to the Secretary of

DHEW. S1713 does not meet these needs as well as H.R. 11192 seems to do.

2. Do we agree with the conclusion of the Federal Interagency Committee on Recombinant DNA Research (March, 1977) that no present authority is sufficient to deal with recombinant DNA techniques in every regard? Yes. As we discussed in detail before your Subcommittee on November 8, only Section 361 of the Public Health Act has the potential to meet this broad mandate. However, 361 does not meet every aspect of the situation, as will be explained in the next few questions.

3. Could Section 361 be used to cover the private sector? Yes.

4. What problems might arise from use of Section 361 to regulate recombinant DNA research? One concern often raised is the notion that invoking Section 361 would seem to some to acknowledge a significant risk of transmission of communicable disease. Present evidence makes such risks strictly conjectural. Section 361, of course, was not written to regulate research. Its use in this regard may provide precedent for broad intrusions into the research environment, with Congressional debate. Section 361 does not deal with hazards to the environment that can be shown to have no primary or secondary effect on human health.

5. What are the authorities of the Secretary under Section 361? For a comprehensive analysis, you should inquire of the General Counsel at DHEW. Probably you have done so already. Our own review suggests that Section 361, together with Section 368, provides broad statutory authority for the development of detailed regulations for essentially all of the functions you name.

6. Compare the authority of the Secretary under Section 361 with that under the currently proposed legislation. In the absence of detailed analysis from DHEW on Section 361, such a comparison is not feasible. Certainly, authorities would be far more explicit under the specific bills than under Section 361.

7. Does the Secretary have authority under Section 361 to preempt State and local actions concerning recombinant DNA research and related activities? The Secretary apparently would *not* have the authority to preclude State or local actions more stringent than the national standards or regulations.

I hope that these responses are helpful to you in the current deliberations.

Yours sincerely,

FRANK PRESS, *Director.*

APPENDIX

List of Witnesses

(In order of appearance)

Philip Handler, President, National Academy of Sciences
Paul Berg, Wilson Professor of Biochemistry, Department of Biochemistry, Stanford University Medical Center
Jonathan Alan King, Associate Professor of Molecular Genetics, Department of Biology, Massachusetts Institute of Technology
Roy Curtiss, III, Senior Professor of Microbiology, Department of Microbiology, University of Alabama
Bruce R. Levin, Associate Professor of Zoology, Department of Zoology, University of Massachusetts
Clifford Grobstein, Professor of Biological Sciences and Public Policy, University of California at San Diego
Daniel Callahan, Director, The Hastings Center Institute of Society, Ethics and the Life Sciences
Marshall S. Shapo, Professor of Law, University of Virginia
Marc Lappé, Chief, Office of Health, Law and Values, Department of Health, California
Frank Press, Director, Office of Science and Technology Policy, Executive Office of the President
Donald S. Fredrickson, Director, National Institutes of Health, Department of Health, Education, and Welfare
Margaret Mead, Emeritus Curator, American Museum of Natural History
William Rutter, Chairman, Department of Biochemistry and Biophysics, University of California, San Francisco
Herbert Boyer, Professor of Biochemistry, Department of Biochemistry and Biophysics, University of California, San Francisco
Harlyn Halvorson, Director, Rosensteil Medical Sciences Research Center, Brandeis University
Oliver Smithies, Leon J. Cole Professor of Genetics, University of Wisconsin
Joseph A. Keyes, Director, Division of Institutional Studies, American Association of Medical Colleges
Frank Young, Chairman and Professor, Department of Biology, University of Rochester Medical Center
Marcia Cleveland, Attorney, Natural Resources Defense Council
Scott Thacher, graduate student in Biochemistry, Harvard University
Susan Wright, Lecturer in the History of Technology, Department of Humanities, College of Engineering, University of Michigan
Robert Corman, Attorney, Assistant Deputy Public Advocate, Department of the Public Advocate, State of New Jersey
Arthur Schwartz, Department of Mathematics, University of Michigan
Joseph Stetler, President, Pharmaceutical Manufacturers Association
Joseph Grady, Research Head, Department of Infectious Disease Research, Upjohn Company
Ronald E. Cape, President, Cetus Corporation
David Newburger, Assistant Professor of Law, Washington University School of Law

List of Additional Statements and Communications in the Hearing Record

Statements:

Council of Scientific Society Presidents, Resolution, August 4, 1977
Nelkin, Dorothy, Program on Science, Technology and Society, Cornell University, November 2, 1977

Newman, Stuart A., Professor, Department of Biological Sciences, State University of New York at Albany, November 29, 1977
Sinsheimer, Robert, Chancellor, University of California at Santa Cruz, December 5, 1977

Communications from:

Burris, Robert H., Professor of Agricultural Biochemistry, and Waclaw Szybalski, Professor of Oncology, University of Wisconsin, December 2, 1977
Cohen, Stanley N., Professor of Medicine and Genetics, Stanford University Medical Center, October 27, 1977
Hess, Eugene L., Executive Director, Federation of American Societies for Experimental Biology, November 29, 1977
Hyland, William F., Attorney General, State of New Jersey, December 15, 1977
Lennette, Edwin H., President, Tissue Culture Association, November 30, 1977
Magee, P. T., Chairman, Department of Microbiology and Public Health, Michigan State University, December 5, 1977
Shapiro, James A., Department of Microbiology, University of Chicago, November 10, 1977
Szybalski, Waclaw, Professor of Oncology, University of Wisconsin, January 4, 1978
Goldstein, Richard, Department of Microbiology, Harvard University School of Medicine, to Donald Fredrickson, Director, National Institutes of Health, August 30, 1977
Gorbach, Sherwood, Professor of Medicine and Microbiology, Tufts University School of Medicine, to Donald Fredrickson, July 14, 1977
Redys, John, Director, Laboratory Division, Department of Health, State of Connecticut, to Pamela Lippe, Friends of the Earth, November 7, 1977
Sullivan, Clare D., graduate student, Harvard School of Public Health, to Donald Fredrickson, December 29, 1977

EXECUTIVE OFFICE OF THE PRESIDENT,
OFFICE OF SCIENCE AND TECHNOLOGY POLICY,
Washington, D.C., January 27, 1978.

Hon. ADLAI E. STEVENSON,
U.S. Senate,
Washington, D.C.

DEAR SENATOR STEVENSON: Thank you for your letter of November 29 and for the opportunity to testify before your Subcommittee on November 8 about recombinant DNA research and applications.

You have raised searching questions about the appropriateness and usefulness of Section 361 of the Public Health Service Act as a basis for the issuance of regulations covering recombinant DNA activities. You are aware, I know, that the Department of HEW's Office of General Counsel, which must rule on the applicability of Section 361, took the position a year ago that there are flaws in the use of Section 361. Most of the analysis of existing authorities, therefore, was directed at the Toxic Substances Control Act and the Occupational Safety and Health Act, as reported in the Interagency Report of March 15, 1977. The language of Section 361, dealing with "quarantine" and with such communicable diseases as smallpox, cholera, yellow fever, and plague has certainly put off many policymakers and scientists. Dr. Omenn's comments, to which you refer, do indeed reflect a concern that use of Section 361 might imply that the strictly speculative hazards associated with DNA research may be real.

Since our November testimony, Dr. Omenn has looked into the background of the uses of Section 361, with the assistance of Mr. Peter Hutt, formerly Assistant General Counsel of HEW and Chief Counsel for the FDA. A copy of Mr. Hutt's detailed report is attached. It is clear that Section 361 has been utilized for a remarkable variety of relatively benign and even non-infectious threats to the public health. Its applicability to the private sector and to intrastate activities has been established in Federal courts. Its applicability to effects on plants, animals, or other components of the general environment seems adequate, so long as there is any possibility of further transmission of effects to humans. Most important, Section 361 has been applied to practices and facilities such as shellfish beds, pet turtle production, importation of nonhuman primates,

production of milk, and standards for water in a way that clearly establishes the preference for prevention of the occurrence of any risk, rather than control of the spread of infection. It is our understanding that the NIH Guidelines on Recombinant DNA Activities are directed at exactly the same objective: to assure that risks of infection being released be eliminated by stringent control over practices and facilities.

Thus, we have raised to an interagency group, including representatives of the Office of the General Counsel of DHEW, the potential applicability of Section 361 in the event that the Congress decides that legislation specific to DNA research cannot be agreed upon and that use of Section 361 is necessary. This single authority, with DHEW the clear lead agency, might well be adequate. We do agree with HEW, of course, that Section 361 was not written for the purpose of regulation of research or even of research applications and that extensive justification and detailed regulations would be required. Such regulations would be required under proposed legislation, as well. We understand that HEW prefers specific Congressional authorization and that Congressman Rogers is reviewing the Administration's proposals along with other alternatives.

Now let me turn to the other two issues you raised.

Issue No. 2

The Department of Commerce activities are progressing satisfactorily. Staff from their Office of General Counsel and from the Office of Environmental Affairs, under Assistant Secretary Baruch, and staff from my Office have met several times with representatives of the Pharmaceutical Manufacturers Association and certain industrial firms. Meetings with labor officials and with representatives of environmental groups are being scheduled. The activity I mentioned above about use of Section 361 and the discussion of new legislation in the Congress has complicated the context of their inquiries, but they are going ahead. Surveillance mechanisms under discussion include registration, biohazards/biosafety committees with public members, and sanctions for violations of guidelines.

Issue No. 3

The preemptions provided in S. 1217 (now withdrawn by Senator Kennedy) and in Amendment 754 by Senator Nelson were introduced, I presume, to clarify responsibility for establishing regulations under any new legislation pertaining to DNA activities. Since the Secretary of HEW would be charged with the implementation of the Act, the Secretary could instruct FDA to require evidence of compliance with DNA regulations in order to approve new drug applications. The NIH Guidelines, as revised, will meet the needs of the Department of Agriculture, we are advised. OSHA reserves the possibility of entering into this matter later, if evidence of significant hazard to employees should arise. NIH guidelines and any regulations developed under new legislation or under Section 361 seem adequate for the workplace at present.

Therefore, we see no present need for changes in other statutes. Nor is there any apparent need to preempt existing statutes.

In closing, let me add that the recombinant DNA work seems to be progressing well and safely, with additional information during the past year that has permitted more sober and realistic discussion of the potential risks. These risks now seem sufficiently low and the NIH Guidelines sufficiently stringent that the public should be much reassured. Furthermore, I believe that the NIH has very effectively engendered public discussion, and I see little indication for a public commission to enhance or possibly reignite the debate of the past few years on this subject.

We are eager to work with you and with other Committees of the Congress in following the development of this research and its applications.

Yours sincerely,

FRANK PRESS, *Director.*

Attachment

COVINGTON & BURLING,
Washington, D.C., January 6, 1978.

GILBERT S. OMENN, Ph. D., M.D.,
Assistant Director for Human Resources and Social and Economic Services, Office of Science and Technology Policy, Washington, D.C.

DEAR GIL: As you requested, I have reviewed the background of Section 361 of the Public Health Service Act (42 U.S.C. 264), its interpretation and application by the Food and Drug Administration and the Public Health Service over

the past several years, and its interpretation by the courts. Enclosed is a copy of each of the documents to which reference is made in this letter, to facilitate your own evaluation.

I

The original Federal communicable disease law was passed by Congress in 1893 (27 Stat. 449). As you will see, Section 3 authorized the Supervising Surgeon-General of the Marine Hospital Service, Department of the Treasury, to issue regulations to prevent the introduction of contagious and infectious diseases into one state from another. Unfortunately, I have not had the opportunity to research and review the legislative history of this Act, and therefore cannot provide information on the specific congressional intent. It appears from the wording of the statute itself, however, that the Department of Treasury was given very broad and all-encompassing authority to prevent the spread of disease.

II

In 1944 Congress consolidated and revised all of the laws relating to the public health service in the Public Health Service Act (58 Stat. 682). (A copy of relevant portions of the House Report on that bill, as reproduced in 1944 U.S. Code and Congressional Service 1211, is enclosed. Section 361, which was later codified in the United States Code as 42 U.S.C. 264, is discussed on pages 1214 and 1234–1235.)

As you know, Section 361, as enacted in 1944, provides broadly that:

"(a) The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary."

In addition, Section 368(a) provides that "Any person who violates any regulation prescribed under sections 361 . . . shall be punished by a fine of not more than $1,000 or by imprisonment for not more than one year, or both."

The wording of Section 361 is uniquely broad. By its terms, this provision authorizes HEW to promulgate any regulations necessary to prevent communicable disease, and to provide for inspection and any other enforcement measures that may be necessary. The legislative history does not detract from the broad statutory language. The House Report states that the "confusing limitations" in the 1893 Act were intentionally eliminated and that the new law was intended to "expressly sanction the use of conventional public-health enforcement methods" as well as to "authorize destruction of contaminated articles or infected animals which are dangerous to man, in those cases where no other disposition is safely possible."

Thus, there is no tenable argument that Section 361 was intended narrowly to be limited only to quarantine of human beings or humans and animals (since the law encompasses all "articles," a term commonly used in regulatory statutes to encompass all substances or objects of any kind), nor is there any argument that inspection is not permitted (since it is specifically mentioned) or that a wide range of other enforcement mechanisms is not authorized (since the law permits any "other measures" for carrying out and enforcing any regulations as in the judgment of HEW may be necessary).

III

Questions have been raised about the application of Section 361 to intrastate (as contrasted with interstate) commerce. Questions have also been raised as to whether Section 361 can be interpreted to authorize the prohibition (as contrasted with the regulation or control) of specified activity. Both of these issues have now been definitively resolved in a 1977 court decision upholding the legality of an FDA regulation banning all small pet turtles from both intrastate and interstate commerce under the sole authority of Section 361.

In the Federal Register of April 7, 1972 (37 F.R. 7005), FDA proposed a prohibition of the importation of small pet turtles, and a requirement of bacterio-

logical testing and certification for interstate shipment of such turtles, in order to prevent the spread of salmonella. This regulation was made final in the Federal Register of November 18, 1972 (37 F.R. 24670).

On the basis of additional information showing that the certification program was not effective, FDA issued two additional alternative proposals in the Federal Register of May 28, 1974 (39 F.R. 18463) that would either prohibit the sale and other distribution of small pet turtles or would improve the certification scheme and impose additional requirements on the sale and shipment of these turtles. In discussing the first of his two alternative proposals in the preamble, the Commissioner stated that:

"Under the Public Health Service Act, the Commissioner has the authority to extend a prohibition on distribution of all turtles and turtle eggs, whether or not they have passed through interstate commerce, if in his judgment such a complete ban would be necessary for effective control over the interstate spread of turtle-associated diseases." (39 F.R. at 18464.)

On the basis of the comments received, the Commissioner issued a final regulation in the Federal Register on May 23, 1975 (40 F.R. 22543), banning all such turtles from intrastate and interstate commerce. In paragraph 13 of the preamble, on page 22545, the Commissioner specifically rejected a suggestion that the turtles should be banned from interstate shipment but should be permitted for intrastate shipment.

Subsequently, the State of Louisiana brought suit to enjoin enforcement of this regulation on a variety of legal grounds. In *State of Louisiana* v. *Matthews*, 427 F. Supp. 174 (E.D. La. 1977), the Court upheld the legality of the regulation against all challenges. Specifically, the Court ruled that FDA could properly ban all small turtles rather than only those turtles shown to be infected and thus to be health hazards, on the ground that "Congress has granted broad, flexible powers to Federal health authorities who must use their judgment in attempting to protect the public against the spread of communicable disease." The Court rejected, as unproven, a contention that less drastic means of regulation would be sufficient to protect the public. It ruled that Section 361 permits FDA to control intrastate as well is interstate activity. Finally, it rejected a contention that the regulation is discriminatory because there are no other comparable regulations. For another court decision broadly upholding the discretion of HEW to enforce Section 361 see *United States* v. *Shinnick*, 219 F. Supp. 789 (E.D. N.Y. 1963).

IV

Section 361 has been applied by the Public Health Service and FDA in the past in a wide variety of ways. In general, the Public Health Service was responsible for implementation of Section 361 until the late 1960s when responsibility for implementation of its foreign aspects were delegated to CDC and for implementation of its domestic aspects relating to the law enforcement functions of FDA were delegated to FDA. (Copies of the current regulations issued under Section 361 by the Public Health Service in 42 C.F.R. Parts 71 and 72, and by FDA in 21 C.F.R. Parts 1240 and 1250, are enclosed. Do not be misled by the citation, as legal authority for these regulations, of Section 215 of the Public Health Service Act; that provision merely authorizes HEW to issue regulations to implement the Public Health Service Act.)

As you will see, these regulations cover a wide variety of subjects. They deal in detail with the sanitation of interstate conveyances. The Drinking Water Standards in 42 C.F.R. 72.201–207 relate not just to bacteriological quality, but also to physical and chemical characteristics which surely would not fall within any narrow definition of the concept of a "communicable disease." The Drinking Water Standards have been enforced as the national standard since 1962.

Etiologic agents are defined, and their transportation regulated, under 42 C.F.R. 72.25. Psittacine birds, lather brushes, and plain garbage are regulated under 21 C.F.R. 1240.65, 1240.70, and 1240.75, as a prophylactic measure to prevent disease.

For many years, the Public Health Service, and more recently FDA, has engaged in joint programs with State and local government agencies and with the regulated industry to promote sanitation in the production of milk products and shellfish, and in the provision of food in eating establishments, under the general provisions of Section 361. Development of the Pasteurized Milk Ordinance and Code, through the Interstate Milk Shippers Conference, has had a major impact on milk sanitation. The PMO provides detailed requirements for the handling of milk and dairy products on the farm, in order to prevent the possi-

bility of communicable disease. The growing conditions for shellfish have similarly been the subject of control since 1924 under the National Shellfish Sanitation Program, and FDA has proposed to establish regulations codifying this program in the Federal Register of June 19, 1975 (40 F.R. 25916), which are now being held in abeyance pending further study required by Congress in Section 16(b) of P.L. 94-370 (90 Stat. 1013, 1033). FDA proposed to codify its 40-year history of cooperation on food sanitation programs for food service establishments in the Federal Register of October 1, 1974 (39 F.R. 35438), and has since concluded instead to issue a model ordinance as announced in the Federal Register of March 22, 1977 (42 F.R. 15428). Under the same authority, FDA has announced a proposed Model Retail Food Store Sanitation Ordinance in the Federal Register of October 25, 1977 (42 F.R. 56367) and a Model Vending of Food and Beverages Ordinance in the Federal Register of October 7, 1977 (42 F.R. 54626).

Finally, in a variety of regulations in the past few years designed to implement a national blood policy, FDA has utilized Section 361 to control blood banking and blood labeling practices in intrastate as well as interstate commerce. The preambles to these regulations specifically mention the need for close control of all blood practices, in minute detail, in order to prevent communicable disease. Copies of the proposed regulations to establish current good manufacturing practice for blood and blood components published in the Federal Register of May 28, 1974 (39 F.R. 18614) and to require a label statement to distinguish volunteer from paid blood donors published in the Federal Register of November 14, 1975 (40 F.R. 53040), both of which discuss this subject, and both of which provide extraordinary detailed requirements, are enclosed.

V

Questions have been raised about the degree and nature of the potential harm that must be shown in order to invoke the authority of Section 361. It appears that the language of the statute itself, its legislative history, and the court opinion interpreting it, place broad discretion in HEW to determine when the scientific evidence warrants reliance on Section 361 to prevent the possibility of communicable disease. Absent evidence that the HEW decision is wholly irrational, it is highly likely that the courts would uphold this exercise of discretion.

Nor is there any limitation in Section 361 on the source from which the potential harm must come in order to justify regulation. The terms of Section 361 permit regulation of research or of commercial activity. Indeed, the present regulations governing transportation of etiologic agents directly affects basic research, and a number of regulations affect commercial activity. The law permits control of human beings, animals, plant material, and any other form of article, in order to prevent communicable disease.

With specific reference to research on recombinant DNA molecules, the question has been raised whether there is sufficient danger of communicable disease to justify invocation of Section 361. If indeed there is no significant possibility of this occurring, it is difficult to understand why the United States Congress, NIH, the entire scientific community, numerous state legislatures and city councils, and many citizens groups, have been spending such an inordinate amount of time debating it. The very nature of the controversy itself is sufficient, in my judgment, to establish the potential for harm that is required under Section 361. If that potential were agreed not to exist the entire issue of regulatory control over this research would never have been raised in the first place.

More specifically, some have questioned whether controls over certain types of research on recombinant DNA molecules, such as research on plant materials, can be justified under Section 361, since arguably the need for control arises from potential communication of disease from one plant to another rather than to man. Others have argued, however, that so little is known about research on recombinant DNA molecules that there is indeed a danger, which will remain until further experimentation proves otherwise, that research on plant materials could unleash pathogenic organisms to infect man, or could otherwise result in human infection in ways we cannot anticipate. Again, the mere existence of this controversy, which has been sufficient to engage the attention of the entire country, seems quite enough to provide a legally sufficient basis for invoking Section 361. Moreover, once jurisdiction is established the courts have held that the National Environmental Policy Act provides substantive authority over all

environmental aspects of the matter. *Environmental Defense Fund, Inc.* v. *Matthews*, 410 F. Supp. 336 (D.D.C. 1976).

It is important, once again, to understand that Section 361 was intended by Congress broadly to authorize prophylactic public health measures to prevent disease before it occurs. All that is needed to support regulations under this provision is either apprehension or uncertainty about the possibility of potential harm, the lack of adequate information showing that the harm cannot occur, and the possibility that the harm would be serious (e.g., irreversible) if it did occur. The more serious the nature of the potential harm, the less is required in the way of apprehension of uncertainty about that harm in order to justify invoking regulatory controls under Section 361.

VI

Questions have also arisen about enforcement of any regulations issued under Section 361. Section 361 itself provides that any articles not in compliance with such regulations may be destroyed, and authorizes any other enforcement measures that may be concluded to be necessary. In initially promulgating its turtle regulations, FDA included a requirement for bacteriological testing and certification. In its proposed shellfish regulations, other enforcement mechanisms were included. Each of the PHS and FDA regulations issued under Section 361 has its own tailor-made enforcement provisions.

It seems clear that the statute authorizes regulations that require destruction of any materials resulting from activity not in compliance with regulations issued under Section 361. There is judicial authority for proposition that a Federal court, using its broad equitable powers, may enjoin violation of any validly-promulgated government regulation. Section 368 specifically provides for a fine and/or criminal incarceration. Section 361 specifically mentions authority for inspection as an enforcement tool. Administrative provisions requiring reports or imposing other enforcement mechanisms are also clearly authorized. Thus, it appears that there is an infinite variety of enforcement mechanisms available, and that any of a number could be incorporated into a regulation promulgated under Section 361.

VII

Questions have been raised about the way in which the recombinant DNA research guidelines could be enforced if they were proposed and promulgated as regulations under section 361. Clearly, it would not be necessary that the same government agency issue the regulations and enforce them. It would be possible, for example, for NIH to issue the regulations (as it presently does), and for CDC to enforce them. I mention CDC because it has jurisdiction over the Clinical Laboratories Improvement Act and thus has experience in inspection and enforcement with respect to scientific laboratories. FDA might also be in a position to enforce the regulations, but its other responsibilities are so overwhelming that enforcement of recombinant DNA research regulations might better be performed by CDC.

VIII

At the recent NIH meeting, representatives of the pharmaceutical industry stated that industry intends to comply with the NIH guidelines and would have no objection to making them mandatory if certain specific problems were overcome. The principal problem involved their concern about submission of trade secret information to NIH. I stated at that meeting that this issue exists with respect to all regulatory agencies, and that FDA, EPA, and the others have resolved it without significant difficulty.

A Federal statute, 18 U.S.C. 1905, explicitly provides that trade secret information provided to the government may not be released to the public by any government employee under pain of criminal penalty. FDA—which regularly receives trade secret information from the regulated industry with respect to food additives, new drugs, biological products, medical devices, and so forth—has issued extensive regulations providing that such trade secret information will be held in confidence by the agency and will not be released to the public. Enclosed is a copy of 21 C.F.R. Part 20, dealing generally with the release of information from FDA to the public, together with Section 314.14 relating to information in IND and NDA submissions (as an example of the way in which this information is handled). The court have now definitely held that 18 U.S.C. 1905 does in fact protect all trade secrets from public disclosure by government agencies. Thus, all

that is needed to resolve this concern of industry is to incorporate some of the routine practices for protection of trade secrets, that have long prevailed in other governmental agencies, into the regulations governing recombinant DNA research.

Sincerely yours,

PETER BARTON HUTT.

See page 73 for letter of Secretary Califano, February 27, 1978, to Senator Stevenson.

U.S. ENVIRONMENTAL PROTECTION AGENCY,
Washington, D.C., December 9, 1977.

Hon. ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space, Committee on Commerce, Science, and Transportation, U.S. Senate, Washington, D.C.

DEAR MR. CHAIRMAN: I am writing in response to your letter of November 30, 1977, which focused on various policy issues associated with recombinant DNA activities. Your particular concern was the extent to which the Environmental Protection Agency (EPA) can regulate the commercial applications of recombinant DNA research under the authorities contained in the Toxic Substances Control Act (TSCA).

I am in general agreement with your observations concerning the scope of TSCA and its application to the commercialization of chemical substances. However, I believe that effective regulation of all aspects of recombinant DNA research—including the commercial applications which may be derived therefrom—would be better achieved by the enactment of comprehensive legislation specifically addressing itself to the unique policy issues surrounding all recombinant DNA activities.

There are two principal factors underlying this recommendation. First, EPA's administration of TSCA is still in its infancy. The Agency is wrestling with the many difficult policy issues involved in the implementation of TSCA, resolution of which may take months or perhaps years. This effort will require a great commitment of Agency resources, and is critical to the ultimate success of the program. Regulation of recombinant DNA activities, however, will require consideration of additional questions which may not be directly relevant to other aspects of the regulation of toxic chemicals; resolution of those issues will require a significant diversion of Agency energy and expertise. As a matter of overall program priorities, therefore, I believe that regulation of all recombinant DNA activities should be placed under some statutory authority other than TSCA.

Second, any attempt to regulate the commercial applications of recombinant DNA research under TSCA may be hampered or obstructed by certain interpretative and conceptual problems. For instance, although there is a general consensus that recombinant DNA molecules are "chemical substances" within the meaning of section 3 of TSCA, it is not at all clear whether a host organism containing recombined DNA molecules fits—or was intended to fit—that definition. Practical applications of recombinant DNA technology will utilize several generations of organisms which will inherit the implanted genetic information via natural biological reproductive processes. If such organisms are subject to TSCA on the grounds that they are a "combination of . . . substances occurring in whole or in part as a result of a chemical reaction," the Agency might logically have to include all living things in the definition of "chemical substance"—an interpretation which I am confident the Congress neither contemplated nor intended.

Similarly, with respect to products which may be derived from such organisms (e.g., enzymes), section 5 of TSCA will require a pre-manufacturing notice only if the product is a "new chemical substance" or will be put to "a significant new use". New methods (including recombinant DNA technologies) of production of chemical substances included in the inventory published under section 8 of TSCA are not per se subject to the notice requirements of section 5. Finally, it should be observed that a significant area of application of recombinant DNA research is likely to be in the economical and efficient production of certain drugs or pharmaceuticals, which are specifically excluded from the coverage of TSCA.

I do not believe that these and similar problems should be solved by amendments to TSCA. As illustrated above, adjustments to particular provisions of TSCA to embrace circumstances peculiar to recombinant DNA research may have

much broader—and undesired—impacts upon the overall regulatory program for toxic substances. Rather, I believe that it would be more appropriate to enact comprehensive legislation regulating all aspects of recombinant DNA research—including all commercial applications—which would be sensitive to the unique problems and issues attendant to this frontier of science.

In closing, however, I would like to emphasize that in the absence of legislation which specifically addresses the unique problems associated with recombinant DNA research, the Agency will conscientiously attempt to protect the public to the fullest extent necessary against any unreasonable risk of injury to health or the environment which may be presented by any recombinant DNA activity, utilizing TSCA and other existing authorities.

Sincerely yours,

DOUGLAS M. COSTLE,
Administrator.

U.S. DEPARTMENT OF LABOR,
OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION,
Washington, D.C., December 15, 1977.

Hon. ADLAI STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space, Committee on Commerce, Science, and Transportation, U.S. Senate, Washington, D.C.

DEAR MR. CHAIRMAN: This will respond to your letter of November 30, 1977 to Secretary of Labor Ray Marshall concerning the authority of the Occupational Safety and Health Administration as it pertains to recombinant DNA.

Generally, the Occupational Safety and Health Act of 1970 covers employees engaged in both DNA research and commercial activities. However, employees of State and local governments such as a State university or community college, are not covered under the Act unless the State has an approved OSHA plan. Nonetheless, research or other activities conducted by a private employer under a contract with the federal, State or local government are, like those of any private employer, subject to the OSH Act. In addition, protection of Federal agency employees is provided for under a special section of the Act which requires Federal agency heads to develop and implement occupational safety and health programs for their employees.

With respect to the regulatory authority of other Federal agencies, section 4 (b) (1) of the Act provides that OSHA shall not apply to any hazardous working conditions that are addressed by the standards or regulations of another agency and which are promulgated by that agency in the "exercise" of its statutory authority. The Committee-reported DNA bill, S. 1217, contains the following provision which is designed to ensure that section 4(b) (1) of the Act would not, in the case of DNA-related activities regulated under the terms of the bill, displace the application of OSHA to working conditions involving DNA.

"(c) This title shall not affect the authority of the Secretary or the Secretary of Labor to exercise their respective authority pursuant to the Occupational Safety and Health Act of 1970. And provided further, that in exercising authority under this title, the Secretary, the Commission, or any person acting on behalf of the Secretary or Commission or pursuant to the provisions of this title, shall not, for the purposes of section 4(b) (1) of the Occupational Safety and Health Act of 1970, be deemed to be exercising statutory authority to prescribe or enforce standards or regulations affecting occupational safety and health."

Thus, OSHA would be the agency with primary statutory responsibility in matters dealing with occupational safety and health hazards of DNA.

While OSHA's present capability to protect workers from the hazards associated with recombinant DNA is limited, this Agency's responsibility for worker health and safety makes it essential for OSHA to acquire appropriately qualified personnel and technological capabilities. The acquisition of this expertise will be crucial in OSHA's effectively setting and enforcing occupational safety and health standards to protect men and women working with recombinant DNA.

I hope this information clarifies OSHA's role in protecting workers from possible hazards of exposure to recombinant DNA. If you need further information, please feel free to contact me.

Sincerely,

EULA BINGHAM,
Assistant Secretary, Occupational Safety and Health.

DEPARTMENT OF AGRICULTURE,
OFFICE OF THE SECRETARY,
Washington, D.C., December 23, 1977.

Hon. ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space,
U.S. Senate, Washington, D.C.

DEAR MR. CHAIRMAN: This is in reply to your inquiry dated November 30, 1977, regarding authorities to regulate products of DNA research and microbes or other organisms containing recombined DNA. Specifically, you requested to be advised whether the Animal and Plant Health Inspection Service (APHIS) of this Department has the authority to control microbes or other organisms containing recombined DNA in animals and plants, and whether authority exists to directly control organisms containing recombined DNA.

Since this is a relatively new area of scientific endeavor, and since the end results of DNA research are still mostly conjectural, we cannot specifically point to any statute administered by APHIS which would be definitely applicable to such research. However, there are several statutes which are administered by APHIS which may ultimately be affected by either the end products resulting from DNA research or by organisms containing recombined DNA.

The major programs that are administered by APHIS under which certain products of DNA research or organisms containing recombined DNA could be regulated are as follows:

A. The Animal Quarantine laws, especially 21 U.S.C. 111, 114, 114(b), 123 and 134(a)

The main purpose of these laws is to prevent the introduction into the United States, or the dissemination from one State or Territory or the District of Columbia to another of the contagion of any contagious, infectious, or communicable disease of animals and/or live poultry. Under these laws, the Secretary of Agriculture has the authority to promulgate such regulations and to take such measures as he may deem proper to prevent such introduction or dissemination. Any product of DNA research or any organisms containing recombined DNA which could be classified as such a "contagion" would be subject to the Animal Quarantine laws.

Section 122.2 of Title 9, Code of Federal Regulations, applies specifically to organisms and vectors. It states that no organisms or vectors shall be imported into the United States or transported from one State or Territory or the District of Columbia, to another State or Territory or District of Columbia without a permit. Organisms are defined in section 122.1(e) of Title 9, Code of Federal Regulations as "All cultures or collections of organisms or their derivatives, which may introduce or disseminate any contagious or infectious disease of animals (including poultry)."

B. The provisions of the Virus-Serum-Toxin Act (21 U.S.C. 151, et seq.)

The purposes of this Act, as stated in the Legislative History (See, e.g., Senate Committee Report No. 1288 on H.R. 28283, 62nd Congress) is to prevent "the introduction into the United States of dangerous and worthless viruses, serums, and analogous products for use in the treatment of domestic animals . . . and also for the purposes of controlling the use, by preventing the interstate shipment, of similar dangerous, and worthless products that may be manufactured within the United States".

Therefore, products of recombinant DNA research which could be considered viruses, serums, toxins or analogous products (i.e., veterinary biologics), as well as any recombined DNA containing organisms used to produce them, which are subject to the provisions of the Virus-Serum-Toxin Act, would also be subject to APHIS regulation.

C. The Federal Plant Pest Act, particularly 7 U.S.C. 150bb and 150dd

This law is mainly concerned with the prevention of the dissemination of plant pests in the United States. The Secretary of Agriculture has the authority to prevent the introduction of such pests which are moved from a foreign country into the United States, or interstate. Therefore, any products of DNA research or organisms containing recombined DNA which fall under the category of plant pests would be subject to regulations by APHIS.

There are, of course, other authorities which might have an impact in this area, such as the Federal Meat and Poultry Inspection Acts (21 U.S.C. 601, *et*

seq. and 21 U.S.C. 451, *et seq.*). These laws are mainly concerned with providing wholesome and safe meat and poultry products to the public. Any meat or poultry products which are "adulterated", within the meaning of that term, would come under the prohibitions of said Acts. If such "adulteration" were related to the administration of products resulting from DNA research or to exposure to organisms containing recombined DNA. then the provisions of these Acts could have significance with respect to the area of DNA research.

Sincerely,

BOB BERGLAND, *Secretary.*

THE SECRETARY OF TRANSPORTATION.
Washington, D.C., December 21, 1977.

Hon. ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space, U.S. Senate, Washington D.C.

DEAR ADLAI: Thank you for your letter of November 30, 1977, asking whether the Hazardous Materials Transportation Act (HMTA) provides authority to deal with the transportation hazards of materials associated with recombinant DNA research or its commercial application; and whether the Department has any plans to examine those hazards.

The short answer to both questions is "yes." The Department has been active in the work of the Interagency Committee on Recombinant DNA Research, chaired by the Director of the National Institutes of Helath (NIH), which examined Federal authority that might be used to control the hazards of recombinant DNA research, including transportation incident to research. In the course of examining our own authority under the HMTA, we concluded that the Act was adequate to insure transportation safety when recombinant DNA materials are moved in commerce.

We presently are considering the possibility of publishing a notice of proposed rulemaking which would include a proposal to designate recombinant DNA materials as hazardous materials subject to certain precautions when shipped. In this regard, we expect to follow the course set by existing NIH Guidelines by limiting our concern to "novel recombinant DNA," i.e. DNA segments inserted into species not known to exchange chromosomal DNA by natural processes with the species of origin. Suitable packaging could be required for novel recombinant DNA, such as that now required for shipment of etiological agents. The exact nature of any needed transportation safety requirements will depend on the hazards associated with the particular material. Varying degrees of hazards are recognized by the NIH Guidelines based on the nature of the genetic material involved.

One of the peculiarities of assessing the hazards of novel recombinant DNA is the extent to which those hazards are unknown. However, the Secretary, under the HMTA, is directed to designate as a hazardous material any material which he finds "may pose an unreasonable risk to health and safety or property" when transported in commerce in a particular quantity and form. Thus. a finding that a particular quantity and form of a material may pose an unreasonable risk is sufficient to bring that material under the HMTA.

It is not possible to give you a precise estimate of when a final decision will be made to publish either a notice of proposed rulemaking on recombinant DNA or a final rule. This is a complex, technical field that is in a state of flux. Elements of the scientific community have recently re-evaluated the hazards of recombinant DNA research and suggest that the hazards may be less than initially believed. At the present time, NIH is considering revision of its guidelines and has solicited public comment on its proposals with a notice in the Federal Register. However, as a general matter, we expect that some form of transportation control on novel recombinant DNA materials, whether generated by research or commercial activities, will be established by the Department. We also believe it advisable that such transportation controls as are necessary be established under the HMTA. to avoid difficulties and confusion that may arise from conflicting transportation requirements that State or local governments may impose. Please let me know if you have any further questions or desire an update on our activities in this matter.

Sincerely,

BROCK ADAMS.

23-890—78——8

U.S. DEPARTMENT OF COMMERCE,
THE ASSISTANT SECRETARY FOR SCIENCE AND TECHNOLOGY.
Washington, D.C., May 26, 1978.

Hon. ADLAI E. STEVENSON, III
Chairman, Subcommittee on Science, Technology, and Space,
U.S. Senate, Washington, D.C.

DEAR SENATOR STEVENSON: On November 29, 1977, you wrote me with regard to a request made to the Department of Commerce by Dr. Frank Press, Director of the White House Office of Science and Technology Policy. This request was that the Office of Environmental Affairs in my office explore the feasibility of establishing a program of "voluntary compliance and meaningful surveillance" in the area of recombinant DNA (RDNA) research carried out by the private sector.

During the period between our receiving Dr. Press' request and the present, the Office of Environmental Affairs has consulted at length with industrial representatives and with other Federal agencies.

A preliminary plan was developed for voluntary surveillance of a private sector RDNA program. Several troublesome issues were raised, most of which we believe could have been resolved. However, in the opinion of industry the proposed plan did not contain adequate protection for proprietary information and rights. For this reason, a voluntary surveillance program entirely satisfactory to both industry and Government is unlikely at this time. The Department, however, continues to maintain its contacts with the appropriate industrial representatives.

You also asked for a summary of RDNA research activities in the private sector. As nearly as can be determined, there are now four pharmaceutical manufacturing companies carrying on this research in their own laboratories:

Upjohn Company, Kalamazoo, Michigan.
Hoffman-LaRoche, Inc., Nutley, New Jersey.
Eli Lilly and Company, Indianapolis, Indiana.
Abbott Laboratories, North Chicago, Illinois.

Two companies are suporting research in university laboratories, under contract:

Miles Laboratories, Inc., Elkhart, Indiana.
Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

Three companies, not in the pharmaceutical manufacturing business, are known to be engaged in RDNA research:

Cetus Corporation, Berkeley, California.
General Electric Company, Schenectady, New York.
Genentec Corporation, San Francisco, California.

Other companies, however, are probably preparing to do RDNA research, by building containment facilities and hiring specialized personnel. The private sector picture, therefore, may change considerably over the next few months depending on establishment of standards of operation applied to private institutions.

I shall keep you informed about further developments as they occur.

Sincerely,

JORDAN J. BARUCH.

NATURAL RESOURCES DEFENSE COUNCIL, INC.,
New York, N.Y., December 2, 1977.

Hon. ADLAI E. STEVENSON, III.
Chairman, Subcommittee on Science, Technology, and Space, Committee on Commerce, U.S. Senate, Washington, D.C.

DEAR SENATOR STEVENSON: Enclosed is a memorandum I have prepared which considers existing statutory authority for regulating recombinant DNA.

I have also enclosed a memorandum prepared for me by two patent attorneys, which describes the effect of disclosure on patent rights. Since NRDC believes that full disclosure by industry of its recombinant activities is essential to public decision-making about this new technology, we recommend that your committee consider legislation which will resolve these problems. Specifically we recommend that the patent laws be amended to make it clear that disclosures made pursuant to a recombinant DNA regulatory statute do not jeopardize patent rights. Also the State Department should be asked to seek similar protection of foreign patent rights in international conventions governing patents.

Thank you for allowing NRDC this opportunity to supplement its testimony before your committee.

Sincerely,

MARCIA J. CLEVELAND.

Enclosure.

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45 ROCKEFELLER PLAZA,
New York, N.Y., November 29, 1977.

MARCIA CLEVELAND, Esq.,
Natural Resources Defense Council, Inc.,
122 East 42nd Street, New York, N.Y.

DEAR MARCIA: You have asked us to explain how certain provisions of the patent laws of the United States and other countries may affect proposed legislation relating to recombinant DNA research. The specific area of interest is the relationship between, on the one hand, disclosure requirements needed to implement a regulatory program for assuring the health and environmental safety of recombinant DNA research and, on the other hand, the waiver-by-publication provisions common in national patent systems. This topic is large, and our response is not exhaustive. We hope, however, that it may be a useful first effort.

The United States Patent Act provides, in Title 35, United States Code, Section 102(b), that a person shall not be entitled to a patent for an invention if (a) the invention was . . . described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The "date of application for patent in the United States" is the date on which the inventor, or the assignee of the inventor, submits to the Patent and Trademark Office the written description of the invention that is known as the patent application. In the normal course of events, that date precedes by about two years the date a patent would ultimately issue for that invention.

Therefore, once an invention has been described in a printed publication, placed in public use or offered for sale, a one-year countdown begins. At the end of that year, patent rights to the invention in the United States are irretrievably lost, unless a patent application has already been submitted.

The terms "printed publication", "public use" and "on sale" are, of course, the operational terms in Section 102(b), the terms whose meaning often determines whether a patent that was issued by the Patent and Trademark Office is valid or invalid. An extensive body of decisional law has grown up around those terms. For present purposes there are two significant facts about that body of case law: first, the precise meaning of each of those terms in Section 102(b) is not fixed; and second, those terms cause patent owners a great deal of concern.

The uncertain scope of the terms used in Section 102(b) leads patent owners to act cautiously when they realize that they are skirting the periphery of one of those forbidden acts. This tendency toward caution is encouraged by the fact that, in litigation, alleged infringers regularly claim that the patented invention was in use, on sale or described in a printed publication sufficiently early to destroy the validity of the patent. Pre-trial discovery on the issue can be extensive.

Moreover, the one-year "grace period" included in United States law is not found in the patent laws of all other countries. Several countries, including Italy, France, the Netherlands, Norway, Spain, Sweden and Uruguay, do not give any grace period for acts like those listed in Section 102(b), no matter where in the world those acts occur. In France, for example, no patent may be obtained if the invention "has been made available to the public by written or oral description; by use or by any other means prior to the date of filing of the patent application. . . ." French Patent Law, Article 8.

Since patent applications must be filed in every country in which patent protection is sought, the more severe foreign requirements respecting prior disclosure, use or sale often become controlling. That is, a United States company interested in obtaining worldwide patent coverage on an invention will file a patent application in at least one country before making *any* publication of the invention. (An international convention adhered to by most countries allows subsequent patent applications filed up to a year later in signatory countries to relate back to the filing date of that first application).

For these reasons, patent-oriented entities involved in recombinant DNA research will be uneasy about disclosing information relating to that research

prior to the date on which patent applications directed to the work are filed. Causing this uneasiness will be the possibility that a litigation opponent might allege years in the future that the disclosure constituted a publication, a public use or an offer for sale. The key fact is not the outcome of such an allegation but the present fear of the future possibility. Since a governmental regulatory program presupposes the disclosure of information about intended research before that research is undertaken and therefore well before any patent applications based on the outcome of the research are filed, the patent laws in their present embodiment are not ideally structured to mesh with a recombinant DNA regulatory program.

If in the recombinant DNA area the needs of the government regulatory function could be satisfied by an early and confidential disclosure of information, then a statute so providing should be considered. The difficulty probably lies in assuring that information submitted in confidence remains confidential throughout the regulatory process.

Time constraints force us to stop at this point. If we can be of further help in the future, please do not hesitate to contact us.

Sincerely yours,

STEPHEN D. KAHN.
ALAN D. GILLILAND.

NATURAL RESOURCES DEFENSE COUNCIL, INC., NEW YORK, N.Y.

Re regulation of recombinant DNA under existing statutory authorities.
Date: December 2, 1977.

Memorandum to: Senator Adlai E. Stevenson, Chairman, Subcommittee on Science, Technology and Space.
From: Marcia J. Cleveland, Staff Attorney, Natural Resources Defense Council, Inc.

INTRODUCTION

This memorandum reviews existing statutory authority which might be used to regulate recombinant DNA activities to determine whether they are adequate, and if not, to identify significant omissions. It discussed the Toxic Substances Control Act (TSCA; 15 U.S.C. §§ 2601, *ff.*); the Food, Drug and Cosmetic Act (FDCA; 21 U.S.C. §§ 301 *ff.*); the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA; 7 U.S.C. §§ 136 *ff.*); the Occupational Safety and Health Act (OSHA; 29 U.S.C. §§ 651 *ff.*); the Clean Air Act (CAA; 42 U.S.C. §§ 1857, *ff.*); the Federal Water Pollution Control Act (FWPCA; 33 U.S.C. §§ 1251, *ff.*); the Public Health Services Act (PHSA; 42 U.S.C. § 264); and the National Environmental Policy Act (NEPA; 42 U.S.C. §§ 4321, *ff.*).

This memorandum concludes that existing authorities are not adequate. In addition to specific gaps in each statute, they share some common shortcomings. None of the regulatory statutes (TSCA, FDCA, FIFRA, OSHA, CAA, FWPCA and PHSA) is designed to prevent environmental damage and health hazards which are as poorly understood as those posed by recombinant DNA. The premarket testing statutes (TSCA, FDCA, and FIFRA) are better designed to deal with incomplete scientific information than the pollution control statutes (OSHA, CAA, and FWPCA), but even the testing statutes are of limited value when we know so little about the hazards to be tested for that we cannot have standardized tests, like bioassays for cancer, which dependably evaluate those hazards. Only NEPA, which requires federal agencies to evaluate environmental impacts regardless of the amount of information available, can be applied to recombinant technology in spite of the present state of our knowledge. None of the statutes except NEPA requires technology assessment of recombinant DNA, and NEPA provides only partial review because it applies only to federal actions. Finally, none of the existing statutes provides adequate regulation of research activities.

AUTHORITY NECESSARY FOR EFFECTIVE REGULATION OF RECOMBINANT DNA

This evaluation of existing statutory authority is based on what the Natural Resources Defense Council believes to be essential elements of a regulatory program for recombinant DNA. Such a program must be designed to prevent release of recombinant organisms into the environment and provide a means for society

to decide whether and to what extent it wishes to develop this technology. To achieve these goals the regulatory program must:

1. Apply uniformity to all persons and institutions engaged in recombinant activities.

2. Prevent release of organisms, rather than control emissions or remedy environmental damage after it has occurred. A preventive program is essential, because the consequences of recombinant technology are largely unknown, but likely to be irreversible. Licensing which requires containment facilities and regulates work practices is the most effective form of preventive legislation.

3. Protect the environment as well as human health.

4. Provide continuing evaluation of risks as more information becomes available.

5. Provide technology assessment of proposed uses of recombinant organisms and techniques.

6. Provide public participation in all phases of regulation.

7. Require full disclosure of all recombinant DNA research, development, manufacturing and use.

8. Establish civil liability of institutions engaged in recombinant DNA activities, for injury to individuals exposed to recombinant DNA organisms.

The following discussion of statutes focuses on points 1 through 5. Points 6, 7, and 8 would each require extensive legal research which was not feasible in the time available for preparing this memorandum.

TOXIC SUBSTANCES CONTROL ACT

Although the Toxic Substances Control Act (TSCA) is one of the broadest regulatory programs available, it does not provide uniform regulation of all chemical substances. It is explicitly designed to fill in the gaps left by existing statutes. Consequently, regulation of recombinant activities under TSCA will only be meaningful if supplemented by regulation under other statutes. Even if used in combination with other statutes, TSCA would provide incomplete protection. TSCA only provides for selective testing of chemical substances; many chemicals will be marketed without any evaluation of their safety or environmental impact because there is no requirement under TSCA that every chemical substance be tested for health and environmental impacts before it is used. Any chemical substances can be marketed free of constraints unless EPA takes affirmative action. Also, it may be difficult to apply TSCA to recombinant DNA because most of the regulatory authority depends on an affirmative finding of unreasonable risk. The paucity of concrete information about risks may make it hard to support such a finding. Finally, TSCA does not provide effective regulation of research.

TSCA's strengths are that it provides a vehicle for requiring research into the hazards of recombinant organisms and can be used to require reporting and monitoring of recombinant activities by industry.

Definitions and jurisdiction: Section 3

The regulatory sections of TSCA (§§ 4–8) apply to chemical substances which are manufactured, distributed in commerce, processed or disposed of. A chemical substance is defined as: "any organic or inorganic substance of a particular molecular structure."

Substances subject to the Food, Drug and Cosmetic Act (FDCA) or the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) are excluded from this definition. Manufacture means "import . . . produce, or manufacture." Commerce includes any trade or transportation of a chemical substance. Consequently, TSCA gives EPA jurisdiction over recombinant DNA molecules, any protein or enzyme produced by a recombinant organism as well as restriction enzymes and vectors used in recombinant technology. It also provides jurisdiction over all activities from research through use.

Notice of new chemicals, inventory of existing chemicals: Sections 5(a)(b)(c)(d), (h)(i), 8(a)(b)

The notice, reporting and inventory provisions of TSCA are central to its effectiveness. Unless EPA knows the chemicals it may have to regulate it cannot protect the public from their hazards. Under these requirements, the manufacturer of a chemical substance is required to report its identity, intended uses and whatever is known about its toxicity and environmental impacts. However, re-

searchers are not required to give notice of new substances and small businesses may not be required to report on existing substances. Non-commercial institutions, such as universities, are exempt from both requirements.

Testing orders: Section 4

If EPA concludes that a chemical substance "may present an unreasonable risk of injury to health or the environment" or "may reasonably be expected to enter the environment in substantial quantities or . . . there is or may be significant or substantial human exposure," it can issue an order requiring testing. The terms "unreasonable risk," "substantial quantities," "significant exposure" are not defined precisely in the statute. However, the legislative history indicates that the Administrator is to have broad authority to issue testing orders and that he will necessarily have to act on incomplete information about risks. Given the breadth of the authority under this section, the Administrator would be able to require research into the hazards of recombinant DNA. If such research involves the use of recombinant techniques, the Administrator could use his authority to set testing protocols and require that strict safety procedures be followed.

Interim regulation: Section 5

EPA has the authority to regulate toxic substances while testing is being conducted, but this authority does not apply to persons and institutions exempt from the notice requirements of § 5. This means that TSCA does not authorize any interim regulation of research or non-commercial institutions since they are not subject to the notice requirements.

Permanent regulation under Section 6

Once EPA finds that a chemical substance "will present an unreasonable risk of injury to health or the environment," it can issue a wide variety of orders to prevent that harm. However, the "will present" standard may require more information about the risks of recombinant DNA than is now available and therefore may not allow preventive regulations until far more is known about the consequences of recombinant technology. Also it is not clear that EPA could establish a facilities licensing system or regulate work practices under § 6. However, § 6 can be applied to research and non-commercial activities.

THE FOOD, DRUG AND COSMETIC ACT

The regulatory system of the Food, Drug and Cosmetic Act is based on premarketing approval—i.e. the requirement that a manufacturer demonstrate the safety of his product before it is marketed. Although this is one of the most powerful regulatory tools for protecting human health, it provides only incomplete protection against the hazards of recombinant DNA. First, the FDCA is only designed to protect human and animal health, not the environment. Second, its regulatory provisions apply only at the point that a product is marketed or after; non-commercial activities are not covered at all. Third, only a limited number of products—food additives, color additives, new drugs, new animal drugs, devices and pesticide residues—are subject to premarketing approval. Other substances covered by the act—food, environmental contaminants or other impurities in food and cosmetics—can only be regulated after the fact, if FDA has evidence that they are unsafe. Finally, the FDCA provides no technology assessment. If a product meets the safety and efficacy requirements of the Act, it must be approved regardless of whether risks outweigh benefits or alternatives are available.

Jurisdiction over recombinant organisms or products: Sections 201, 301, 402, 501, 601

The FDCA prohibits the sale in interstate commerce of any adulterated food, drug, device or cosmetic (§ 301(a)). Food is considered adulterated if it "bears or contains any poisonous or deleterious substance which may render it injurious to health" or contains an additive, or residue which does not comply with premarketing approval requirements or tolerances (§ 402). Similarly, drugs and devices are adulterated if they are "injurious to health" or have not complied with approval and quality control requirements or contain unapproved color additives. Cosmetics are adulterated if they contain any "poisonous or deleterious substances" or are not manufactured according to quality control requirements. If recombinant organisms or recombinant DNA molecules themselves are ever used as food, drugs or cosmetics, they could be prohibited under the Act if they

posed a health risk to humans. If as is more likely, recombinant organisms are used to produce food or drugs, these products could be regulated to assure that no harmful, or avoidable residues of recombinant organisms, or DNA molecules, are left in the product.

Premarket approval and pesticide tolerances: Sections 408, 409, 505, 512, 515, 706(a)

All of the premarket approval sections of the Act require the manufacturer to prove the safety and effectiveness of his product and assign him the burden of developing safety and efficacy data. However, these provisions suffer from the same weakness as testing orders under TSCA: the risks of recombinant organisms do not lend themselves to standardized testing for risks. A manufacturer may conduct enough safety testing to satisfy the FDCA, and not uncover a significant hazard because we do not know how to look for hazards. These premarketing approval sections will also have the effect of requiring complete reporting of products made with recombinant techniques, but this reporting will occur too late to permit any effective technology assessment.

Nonpremarketing approval sections: Sections 401, 406, 601

The sections of the FDCA which do not require premarketing approval and safety testing provide virtually no protection against the hazards of recombinant technology. These provisions leave FDA with the burden of showing that a recombinant organism which contaminates a food or cosmetic is injurious to health or avoidable. Both of these requirements will be difficult to meet with our limited knowledge of risks.

Good manufacturing practices, registration of producers of drugs and devices, batch certification of insulin and antibiotics: Sections 505, 506, 507, 510, 512, 515

The FDCA has several provisions which require a drug or device producer to follow good manufacturing practices (GMP's) to insure that the purity of drugs is maintained. These GMP's are specified by regulation and are enforced by a requirement that producers register each facility where drugs and devices are produced. Registered facilities are subject to regular inspection and are required to report regularly which drugs are being produced at that facility. Insulin and antibiotics are subjected to the additional requirement that each batch be certified by FDA to insure that it meets the purity standards established for those drugs. The GMP, registration, reporting and certification provisions of the FDCA provide only limited regulation of recombinant technology, but they may provide a useful model for licensing recombinant research and production facilities.

FEDERAL INSECTICIDE, FUNGICIDE AND RODENTICIDE ACT

FIFRA establishes a regulatory structure very similar to the FDCA. It requires premarketing approval of pesticides, registration of facilities which produce pesticides, and in addition requires certification of users of pesticides. However, FIFRA differs from the FDCA in that approval of a pesticide includes consideration of environmental costs. A pesticide can only be approved if its use "will not generally cause unreasonable adverse effects on the environment." Although this standard provides for cost/benefit balancing, it does not provide the kind of technology assessment necessary for recombinant DNA. The Administrator is not required to consider alternatives to a given pesticide and is specifically prohibited from refusing registration because a pesticide is not essential.

FIFRA would cover any use of recombinant technology for pest control or to promote or regulate the growth of plants. Any micro-organism which imparted nitrogen fixating abilities to plants which do not now have that ability would be covered. However, FIFRA suffers from the same weaknesses as FDCA, it does not regulate research and development, or non-commercial activities, and it presumes that studies can be conducted by an applicant for registration which accurately assess the hazards.

OCCUPATIONAL SAFETY AND HEALTH ACT

OSHA establishes national standards for substances which pose a health hazard to employees and requires all employers to comply with those standards

and provide their employees a place of employment "free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees." States can administer the Act within their borders, as long as they have approved programs at least as strict as the federal program. The principal limitation of OSHA is that it only protects employee health, the health of the general public and the environment are not within scope of the Act and employees of states which do not administer their own OSHA programs are exempt from the Act. This means that researchers at some state universities cannot be covered by OSHA standards. Also, OSHA is designed to apply to health hazards, for which information is already available. Unlike the premarket testing statutes, it is not designed to compel research on hazards which are either unknown or poorly understood. Finally, OSHA contains no provisions for technology assessment. Indeed, it requires that standards promulgated under the Act be feasible. This feasibility requirement presumes that at some point the health of workers may be compromised to insure the continued availability of their products. This kind of compromise should not be available in the regulation of recombinant DNA.

One feature of OSHA is sound and should be incorporated into any regulatory program for recombinant DNA. Standards promulgated under OSHA can require an employer to install control technology, modify work practices and give his employees protective clothing and equipment, changing rooms, showers and lunch rooms. OSHA is the only statute which provides for control of workplace design and work practices.

THE CLEAN AIR ACT AND THE FEDERAL WATER POLLUTION CONTROL ACT

These two acts are primarily designed to remedy existing pollution problems. They establish national standards, which define maximum ambient levels for pollutants and limit discharges from each source. These standards are achieved either by federal enforcement programs or by state programs pursuant to approved plans. Although both these statutes provide comprehensive regulatory programs, they are poorly suited to regulating recombinant DNA. They are designed to regulate pollutants, the health and environmental impacts of which are relatively well understood, rather than a technology the consequences of which are largely unknown. Both the air and water acts place limitations on the discharge of pollutants based on the control technology which is either available or can be developed. They are not designed to completely prevent discharge as is necessary with recombinant DNA. Unlike OSHA they do not regulate work practices, but rather focus on controlling emissions.

THE PUBLIC HEALTH SERVICES ACT

§ 361 of the Public Health Services Act gives the Secretary of Health, Education and Welfare broad dicretion to regulate recombinant DNA technology to protect human health. It empowers the Secretary to: ". . . make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession . . ."

It further provides that: "for purposes of carrying out and enforcing such regulations, the [Secretary] may provide for such inspection, . . . disinfection . . . and other measures, as in his judgment may be necessary."

The problem with the PHSA is that it does not explicitly provide for protection of the environment. In other regulations under this section a communicable disease is defined as "an illness due to an infectious agent or its toxic product . . ." transmitted by persons, animals, plants or the inanimate environment. (42 C.F.R. §§ 71.1(b), 72.1(b)). Another weakness of § 361 is that it leaves the regulatory structure for enforcement to the discretion of the Secretary.

THE NATIONAL ENVIRONMENTAL POLICY ACT

NEPA is the only federal statute that provides for technology assessment. NEPA requires all federal agencies to consider the impact their activities will have on the environment and the alternatives to a proposed action. But even NEPA does not require that nonessential technology be avoided or that the environmentally least damaging alternative must be chosen. Furthermore, NEPA

only applies to recombinant activities regulated or funded by the federal government. Because the federal government's authority to reach private recombinant activities is limited, the value of NEPA as a vehicle for evaluating the consequences of recombinant technology is also limited.

THE LIBRARY OF CONGRESS,
CONGRESSIONAL RESEARCH SERVICE,
Washington, D.C., December 7, 1977.

To: Senate Committee on Commerce, Science, and Transportation, Subcommittee on Science, Technology, and Space.
From: American Law Division.
Subject: Regulation Under Current Law of the Products of Recombinant DNA Research.

In response to your request for a determination as to whether products of recombinant DNA research may be regulated under current federal statutes, we have analyzed the following laws:

1. The Patent Laws (Title 35);
2. Toxic Substances Control Act (15 U.S.C. 2601 *et seq.*);
3. Marine Protection, Research and Sanctuaries Act (33 U.S.C. 1401 *et seq.*);
4. Federal Water Pollution Control Act (33 U.S.C. 1251 *et seq.*);
5. Solid Waste Disposal Act (42 U.S.C. 3251 *et seq.*);
6. Federal Hazardous Substances Act (15 U.S.C. 1261 *et seq.*);
7. Hazardous Materials Transportation Control Act (18 U.S.C. 834 *et seq.*);
8. Occupational Safety and Health Act (29 U.S.C. 631 *et seq.*);
9. National Environmental Policy Act (42 U.S.C. 4321 *et seq.*);
10. Public Health Service Act (42 U.S.C. 201 *et seq.*);
11. Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 *et seq.*);
12. Consumer Product Safety Act (15 U.S.C. 2051 *et seq.*).

In brief, comprehensive regulation of the products resulting from recombinant DNA research techniques does not appear feasible under current laws. At best, regulation will be piecemeal and dependent on the uses for which those products are intended. Regulation will be dispersed throughout several federal agencies, where the research activities involved come under the respective department or agency mandate and it will be limited by the purposes enumerated in the appropriate authorizing legislation.

There has been very recent, rather curious development that could have far-reaching effects in the realm of genetic experimentation. In an October decision, the United States Court of Customs and Patent Appeals, as a matter of first impression, held that a biologically pure culture of a micro-organism, that apparently did not exist as a biologically pure culture naturally, was a "manufacture" within the meaning of the patent statutes. Thus, the fact that the claimed invention was alive did not remove it from the category of patentable things. Two judges dissented from the court's decision and whether the decision will stand upon appeal is a matter of speculation. If it should, then the patent laws may offer the most wide-reaching means of regulating the uses to which DNA research products may be put. See, *Application of Bergy*, U.S. Court of Customs and Patent Appeals, October 6, 1977.

The Constitution confers upon Congress the power to secure authors and inventors, for periods of limited duration, the exclusive right to their writings and discoveries. This power is implemented by legislation which vests an inventor with the right to exclusive use of his invention provided he has perfected his right by proceeding in the manner required by law. (The patent laws may be found in Title 35 of the U.S. Code.)

Ultimately, the decision as to whether new life forms may be patented is a matter for Congress. The Constitution does not spell out the subject matters which are proper ones for patent protection. The exercise of the patent power is a permissive one and Congress may restrict or enlarge the granting of patent rights by specifying categories of discoveries or inventions appropriate for patent protection.

In *Application of Bergy* the court found a new genetic composition to fall within the statutorily recognized category of "manufacture" or an "article of manufacture." While new life forms have not been treated as patentable hereto-

fore, the Supreme Court has simply stated that "to obtain a patent for a product made from raw material, it must possess a new or distinctive form, quality, or property." *American Fruit Growers, Inc.* v. *Brodex Co.*, 283 U.S. 1, 8 U.S.P.Q. 131 (1931). (A thorough discussion of the patent laws is outside the scope of this paper, but for a very good introduction to patent law, see, Peter D. Rosenberg, *Patent Law Fundamentals* (New York, 1975).)

Generally speaking, as the law now stands, regulation of scientific research or its products must be predicated on some legitimate governmental interest such as receipt of federal funding or on a federal power such as Congress's power to regulate interstate commerce. Although legislation may bring within its regulatory ambit all persons engaged in an activity which affects commerce (see, e.g. OSHA, 29 U.S.C. 652 (5)), it is doubtful whether such regulatory authority would extend to private recombinant DNA research conducted by a private individual with very few, if any research associates in a small, local facility. On the other hand, there is no doubt that DNA research may be regulated to some extent (and probably insofar as use of its products are concerned) in research facilities receiving federal funds. Should the patent laws be construed as encompassing the products of genetic research, then federal regulation of DNA research could be predicated on still another federal power.

The Toxic Substances Control Act, effective since October 1976, gives authority to the Environmental Protection Agency (EPA) to ban or restrict the manufacture, processing, distribution, commercial use or disposal of chemical substances and mixtures which will present "an unreasonable risk of injury to health or the environment." 15 U.S.C. 2601. Of the laws we have analyzed, this Act presently has the greatest potential for regulation of DNA research products. Initially however, to be subject to the Act a "processor" of chemical substances or mixtures must be involved in an activity which affects interstate trade, traffic or transportation. 15 U.S.C. 2602 (3)(4). As noted previously, the private, independent researcher conducting an entirely local research activity may not be within the Act's regulatory scope.

Providing this threshold condition is met the Act applies, where there is an unreasonable risk, to the production of a "chemical substance," i.e. "any organic or inorganic substance of a particular identity" which occurs in nature or as a result of a chemical reaction. Any combination of chemical substances which does not occur in nature or as the result of a chemical reaction, i.e. a "mixture," is also subject to the regulatory provisions of the Act provided that "there is a reasonable basis to conclude" that the activity "presents or will present an unreasonable risk of injury to health or the environment." 15 U.S.C. 2605(a). Thus, the EPA may not restrict or ban such chemical substances or mixtures unless the risk is unreasonable. In making that determination the Administrator of the EPA must consider and publish a statement, with respect to the effects and magnitude of the exposure of the substance or mixture, the benefits of its uses and the availability of substitutes and "the reasonably ascertainable economic consequences of the rule, after consideration of the effect on the national economy, small business, technological innovation, the environment, and public health." 15 U.S.C. 2605(c)(1)(A)–(D).

Three key provisions serve to effectuate the EPA's regulatory authority under the Act and are potential methods of regulating DNA products somehow involved in or affecting interstate commerce. First, EPA may require the testing of any chemical substance or mixture if there is potential for an unreasonable risk of injury. 15 U.S.C. 2603(a)(1)(A)(i). The Senate Conference Report indicates that testing may be required wherever "there is a basis for concern." S. Rept. 94–1302, 94th Cong., 2d Sess., at 61. Furthermore, testing may be required if there is insufficient data on which to base a prediction as to the dangers of such substances. 15 U.S.C. 2603(a)(1)(A)(ii)(iii).

The Act also provides for a pre-market review mechanism. Notice to EPA is required prior to the manufacture or processing of any "new chemical substance," but such notice is not required for "mixtures" unless the mixture contains a new chemical substance or is a "significant new use" of an existing chemical substance. 15 U.S.C. 2604 (A mixture is a combination of chemical substances where the combination does not occur in nature or does not result from a chemical reaction.) Nor does the pre-market notification requirement apply to the production of "small quantities" of chemicals to be used solely for research and development, though persons working with such chemicals must be notified of any risks to their health. 15 U.S.C. 2604(h)(3). Furthermore, to come under the provisions,

the manufacture or processing of chemical substances must be "for commercial purposes." 15 U.S.C. 2604(i).

The most far-reaching of EPA's regulatory powers under the Act is its authority to require maintenance of records and submission of reports by processors and manufacturers. 15 U.S.C. 2607. "Small manufacturers and processors" are not covered by this requirement, however other persons who manufacture or process small quantities of mixtures or chemical substances "solely for purposes of scientific experimentation or analysis, etc." must submit reports as the Administrator determines to be necessary. Again, this activity, to be regulated, must affect commerce.

The Act indicates a preference for use of applicable laws other than the Toxic Substances Control Act to regulate chemical hazards where it is possible. 15 U.S.C. 2608 (a) (b). It also requires the Administrator of EPA to cooperate with any other federal agency to achieve maximum enforcement of the Act. Thus, other agencies that regulate chemical hazards, such as the Department of Transportation (transport of hazardous materials), the Consumer Product Safety Commission (safety of consumer products), and the Department of Labor (OSHA), must consult with and coordinate their regulatory efforts with those of the EPA. Where the actions taken by the other agencies or by the Administrator of EPA under other laws provide insufficient protection, then the EPA may have authority to require additional protective measures. More specifically, if the Administrator determines that the risk "may be prevented or reduced to a sufficient extent" by another agency's action, then he must submit a report outlining those risks to the other agency. If the agency determines such a risk does not exist, or it initiates its own action, then EPA is precluded from further action. 15 U.S.C. 2608(a). If, on the other hand, the risks come under laws also administered by EPA such as the Federal Water Pollution Control Act, the Marine Protection, Research, and Sanctuaries Act, the Clean Air Act, the Safe Drinking Water Act, or the Solid Waste Disposal Act, the Administrator may proceed under the Toxic Substances Control Act if he determines that to do so is "in the public interest." That is true even if the "risk could be eliminated or reduced to a sufficient extent by actions taken under" the other law. 15 U.S.C. 2608(b). (For a more detailed analysis of the Act and discussion of some additional provisions, see, Robert F. Zener, "The Toxic Substances Control Act: Federal Regulation of Commercial Chemicals." 32 The Business Lawyer 1685 (July 1977).)

Other federal laws administered by the EPA offer potential authority for limited regulation of DNA research products. Under the Marine Protection, Research and Sanctuaries Act. 33 U.S.C. 1401 et seq., EPA prohibits (or strictly limits) the dumping into ocean waters of "any material which would adversely affect human health, welfare, or amenities, or the marine environment, ecological system, or economic potentialities." 33 U.S.C. 1401(b). The definition of "material" includes "matter of any kind or description, including radiological, chemical, and biological warfare agents, radioactive materials, chemicals, biological and laboratory waste, etc." 33 U.S.C. 1402(c). The Act appears sufficiently broad to encompass disposal of DNA research products. Unless EPA has issued a permit (after notice and opportunity for a public hearing) specifying sites and times, etc., then ocean dumping of dangerous materials as defined by the Act is prohibited. Violations of the Act are punishable by civil penalties and/or criminal fines. 33 U.S.C. 1415(a)(b).

The Federal Water Pollution Control Act. 33 U.S.C. 1251 et seq., while of limited applicability in the regulation of DNA products, prohibits the discharge into navigable waters of pollutants (including toxic pollutants). 33 U.S.C. 1251 (a)(1)(3). Potentially, if a DNA research product should be classified by EPA as a pollutant, the Administrator has authority to restrict and control or prohibit its discharge into the Nation's waters in order "to restore and maintain the chemical, physical, and biological integrity of the Nation's waters." 33 U.S.C. 1251(a).

The Solid Waste Disposal Act. 42 U.S.C. 3251 et seq., administered by EPA, may also be of limited utility in attempts to regulate use and disposition of DNA products. In response to a Congressional finding "that inefficient and improper methods of disposal of solid wastes results in scenic blights, create serious hazards to the public health, including pollution of air and water resources, accident hazards, etc.," one of the purposes of the Act is "to provide for the promulgation of guidelines for solid waste collection, transport, separation, recovery and disposal systems." 42 U.S.C. 3251 (a)(4), (b)(4). Solid waste is defined to include "garbage, refuse, and other discarded solid materials, including

solid waste materials resulting from industrial, commercial, and agricultural operations." 42 U.S.C. 3552(4).

The Federal Hazardous Substances Act, 15 U.S.C. 1261 et seq. gives the Consumer Product Safety Commission authority to regulate labeling and interstate transportation of hazardous and toxic substances intended for household use. The household use condition undoubtedly limits the Act's applicability in the DNA research situation. If the hazardous substance is intended by the manufacturer or producer to be used for non-household commercial or industrial purposes, and is packaged and distributed for non-commercial purposes, it is outside the Act's jurisdiction unless it is actually diverted for household use. Consumer Product Safety Commission Advisory Opinion No. 136 (October 9, 1974). Thus, while the definition of hazardous substance includes any toxic substance "(other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface," to be banned under the Act the substance must be "intended or packaged for use in the household." 15 U.S.C. 1261 (g), (q)(1).

Under the Hazardous Materials Transportation Control Act, 18 U.S.C. 834 *et seq.*, the Department of Transportation has regulatory authority over the interstate transport of explosives, radioactive materials, etiologic agents, and other dangerous articles. The Department is entrusted with formulating regulations, which may be changed on its own motion or upon application by any interested party, for the safe transportation of all listed hazardous materials. A wide-ranging list of materials presently subject to the Act's requirement may be found at 49 C.F.R. Part 17. While the authority of the Department of Transportation does not go to direct regulation of the uses to which DNA products may be put, it may be used to limit and control the extent and manner of dissemination of those products by vehicles which are operated on land by "any for-hire carrier engaged in interstate or foreign commerce." 18 U.S.C. 832(a). Again, as under many federal laws, the non-commercial, independent researcher conducting a private, local experimental facility may not come within the scope of the Act so long as he does not engage commercial vehicles to transport materials he uses or produces.

With respect to the Occupational Safety and Health Act (OSHA), 29 U.S.C. 651 *et seq.*, the Congress expressed, as the basic purpose of the Act, to assure "so far as possible every working man and woman in the Nation safe and healthful working conditions" and provided for the Secretary of Labor to promulgate standards for places and conditions of employment which are free from "recognized hazards." 29 U.S.C. 654. However, the Act specifically excludes State or political subdivision of a State from the definition of employer and while the Act brings within its orbit all employers engaged in a business which affects commerce, it is questionable, here, as under other federal laws, whether OSHA's regulatory authority extends to private recombinant DNA research conducted by an individual with a few employees in a small, local laboratory.

In *Dekle* v. *Todd*, a state court held that OSHA did not apply with respect to a two man farm roof repair job. 207 S.E. 654 (Ga. App. 1974). However, a federal court of appeals did apply the Act to a local building service maintenance supply company which supplied services to businesses engaged in interstate commerce. *Brennan* v. *Occupational Safety and Health Review Commission*, 492 F. 2d 1027 (1974). Thus, OSHA may very well be applicable to recombinant DNA research, generally, so long as there is at least a minimal contact with interstate commerce. It is also probable that the Act will not be applicable to a private researcher conducting experimentation in a small, local research facility, even if he does have a few employees. The Act certainly will not apply absent an employer-employee relationship.

Another aspect of the Act limits its potential utility for regulation of DNA products. Under OSHA, the authority of the Secretary of Labor is limited to recognized hazards and to the working environment. The courts have recognized that protection of the workplace under OSHA extends to those hazards which are identifiable by technical instruments. For instance, a federal court has upheld the use of air sampling pumps to collect contaminants in the air that an employee would normally breathe and the Commission's consequent order that action be taken to reduce the contaminant. *American Smelting and Refining Company* v. *Occupational Safety and Health Review Commission*, 501 F. 2d 504 (1974). However, the contaminant in that case was airborne concentrations of lead and the regulatory requirements were based on a recognized national standard for airborne lead. Thus, *American Smelting* supports the concept that

the regulatory authority of the Secretary of Labor under OSHA extends to airborne contaminants known to be dangerous, but whether OSHA's authority extends to unquantifiable and speculative dangers is certainly questionable. Another federal court relied on the legislative history of the Act in determining that a recognized hazard is one which is known to safety experts in the industry:

An activity may be a "recognized hazard" even if the defendant employer is ignorant of the activity's existence or its potential for harm. The term received a concise definition in a floor speech by Representative Daniels when he proposed an amendment which became the present version of the general duty clause: "A recognized hazard is a condition that is known to be hazardous, and is known not necessarily by each and every individual employer but is known taking into account the standard of knowledge in the industry. In other words, whether or not a hazard is 'recognized' is a matter for objective determination; it does not depend on whether the particular employer is aware of it." 116 Cong. Rec. (Part 28) 3877 (1970). The standard would be the common knowledge of safety experts who are familiar with the circumstances of the industry or activity in question—*National Realty and Construction Company, Inc.* 489 F. 2d 1257 (D.C. Cir. 1973).

It is dubious as to whether a court would uphold authority of the Secretary to promulgate and enforce standards for unknown dangers or hazards so as to prevent the inadvertent escape of an organism with a combination of unknown genetic characteristics. No specific authority was found to support the concept that the Secretary of Labor has authority to issue and enforce standards which would provide protection beyond the immediate working environment, or which would regulate, control, limit or possibly prohibit DNA research or use of its products. Under OSHA, it appears that the authority of the Secretary would be limited to the regulation of working conditions and the environment of employees engaged in such research where there is some relationship to commerce and then that such regulations could extend only to known or recognized hazards.

Presently, the National Environmental Policy Act (NEPA), 42 U.S.C. 4331 *et seq.*, may in effect, have the most far reaching applicability to the initiation and monitoring of DNA experiments. While the Act only requires environmental impact statements (EIS) for federal projects and work conducted with federal grants or loans (40 C.F.R. 1500.5(a)(2)) the requirement does apply to any major federal project with the potential to significantly affect the environment. (40 C.F.R. 1500.6(a)). Currently all National Institutes of Health sponsored DNA research projects are required to submit an EIS assessing:

(i) the environmental impact of the proposed action,

(ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,

(iii) alternatives to the proposed action,

(iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and

(v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented. 42 U.S.C. 4332(2)(C)(i)–(v).

In addition, the regulations require submission of a draft EIS for comment and review by the Council on Environmental Quality (CEQ) and other outside reviewers (including other agencies). While the preparation of an EIS is generally a pro forma exercise and review is usually cursory, the regulations do provide a basis for careful and meaningful monitoring of the proposed activity. To further assure safety of NIH funded DNA experiments, where there appear fundamental risks, the CEQ has authority to issue supplemental guidelines for EIS preparation as are necessary, 40 C.F.R. 1500.14.

Currently, according to a recent newspaper report, virtually all DNA research, some $10 million worth this year, is NIH funded. The Washington Post, Friday, November 18, 1977, p. A–8. Thus, the regulatory potential under NEPA may be one of the most comprehensive means of monitoring, indirectly, the uses to which DNA products are put.

The Public Health Service Act, 42 U.S.C. 264, provides for the promulgation of regulations to prevent the introduction, transmission, or spread of communicable diseases from abroad or from one State into another. Under the Act, the Secretary of Health, Education and Welfare (HEW) is authorized to provide for "such inspection, fumigation, disinfection, sanitation . . . destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous

infection to human beings." 42 U.S.C. 264(a). There are limitations, however, with respect to detention of persons who are believed to be infected with a communicable disease. 42 U.S.C. 264(b)(c)(d). These limitations, apparently, do not apply to articles.

The appropriate HEW regulations, insofar as regulation of DNA products are concerned, control the interstate transportation of "biologic products" and "etiologic agents." The applicable definitional sections are reprinted here for your convenience:

SUBPART C—SHIPMENT OF CERTAIN THINGS

§ 72.25 Etiologic agents.[1]

(a) *Definitions.* As used in this section:

(1) An "etiologic agent" means a viable microorganism or its toxin which causes, or may cause, human disease.

(2) A "diagnostic specimen" means any human or animal material including, but not limited to, excreta, secreta, blood and its components, tissues, and tissue fluids being shipped for purposes of diagnosis.

(3) A "biological product" means a biological product prepared and manufactured in accordance with the provisions of 9 CFR Part 10, Licensed Veterinary Biological Products, 42 CFR Part 73, Licensed Human Biological Products, 21 CFR 130.3, *New drugs for investigational use in humans*, 9 CFR Part 103, Biological Products for Experimental Treatment of Animals, or 21 CFR 130.3(a), *New drugs for investigational use in animals*, and which, in accordance with such provisions, may be shipped in interstate traffic.

(b) *Transportation; etiologic agent minimum packaging requirements.* No person may knowingly transport or cause to be transported in interstate traffic, directly or indirectly any material, including but not limited to, diagnostic specimens and biological products, containing, or reasonably believed by such person to contain, an etiologic agent unless such material is packaged to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling in transportation.

(c) *Transportation; etiologic agents subject to additional requirements.* No person may knowingly transport or cause to be transported in interstate traffic, directly or indirectly, any material, other than diagnostic specimens and biological products, containing, or reasonably believed by such person to contain, one or more of the following etiologic agents unless such material is packaged in accordance with the requirements specified in paragraph (b) of this section, and unless, in addition, such material is packaged and shipped in accordance with the requirements specified in subparagraphs (1)–(6) of this paragraph:

BACTERIAL AGENTS

Actinobacillus—all species.
Arizona hinshawii—all serotypes.
Bacillus anthracis.
Bartonella—all species.
Bordetella—all species.
Borrelia recurrentis, B. vincenti.
Brucella—all species.
Clostridium botulinum, Cl. chauvoei, Cl. haemolyticum, Cl. histolyticum, Cl. novyi, Cl. septicum, Cl. tetani.
Corynebacterium diphtheriae C, equi, C. haemolyticum, C. pseudotuberculosis, C. pyogenes, C. renale.
Diplococcus (Streptococcus) pneumoniae.
Erysipelothrix insidiosa.
Escherichia coli, all enteropathogenic serotypes.
Francisella (Pasteurella) tularensis.
Haemophilus ducreyi, H. influenzae.
Herellea vaginicola.
Klebsiella—all species and all serotypes.
Leptospira interrogans—all serotypes.
Listeria—all species.

[1] The requirements of this section are in addition to and not in lieu of any other packaging or other requirements for the transportation of etiologic agents in interstate traffic prescribed by the Department of Transportation and other agencies of the Federal Government.

Mima polymorpha.
Moraxella—all species.
Mycobacterium—all species.
Mycoplasma—all species.
Neisseria gonorrhoeae, N. meningitidis.
Pasteurella—all species.
Pseudomonas pseudomallei.
Salmonella—all species and all serotypes.
Shigella—all species and all serotypes.
Sphaerophorus necrophorus.
Staphylococcus aureus.
Streptobacillus moniliformis.
Streptococcus pyogenes.
Treponema caretcum, T. pallidum, and *T. pertenue.*
Vibrio fetus, V. comma, including biotype El Tor, and *V. parahemolyticus.*
Yersenia (Pasteurella) pestis.

FUNGAL AGENTS

Actinomycetes (including *Nocardia* species, *Actinomyces* species and *Arachnia propionica*).
Blastomyces dermatitidis.
Coccidioides immitis.
Cryptococcus neoformans.
Histoplasma capsulatum.
Paracoccidioides brasiliensis.

VIRAL, RICKETTSIAL, AND CHLAMYDIAL AGENTS

Adenoviruses—human—all types.
Arboviruses.
Coxiella burnetii.
Coxsackie A and *B viruses*—all types.
Cytomegaloviruses.
Dengue virus.
Echoviruses—all types.
Encephalomyocarditis virus.
Hemorrhagic fever agents, including *Crimean hemorrhagic fever (Congo), Junin,* and *Machupo viruses,* and others as yet undefined.
Hepatitis-associated antigen.
Herpesvirus—all members.
Infectious bronchitis-like virus.
Influenza viruses—all types.
Lassa virus.
Lymphocytic choriomeningitis virus.
Marburg virus.
Measles virus.
Mumps virus.
Parainfluenza viruses—all types.
Polioviruses—all types.
Poxviruses—all members.
Psittacosis-Ornithosis-Trachoma-Lymphogranuloma group of agents.
Rabies virus—all strains.
Reoviruses—all types.
Respiratory syncytial virus.
Rhinoviruses—all types.
Rickettsia—all species.
Rubella virus.
Simian viruses—all types.
Tick-borne encephalitis virus complex, including *Russian spring-summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever,* and *Central European encephalitis viruses.*
Vaccinia virus.
Varicella virus.
Variola major and *Variola minor viruses.*
Vesicular stomatis virus.
Yellow fever virus.

Again, however, these quarantine sections relate only to the shipment of products rather than the uses to which they are put. It is suggested that even if that requirement is met, the Secretary of HEW has no authority to regulate DNA products until they have already been determined to be a "source of dangerous infection to human beings."

The Federal Food, Drug and Cosmetic Act, 21 U.S.C. 301 et seq., provides authority for regulation of the manufacture and interstate transportation of drugs and new drugs. Drug means (among other things) "articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. 321 (g)(1)(c). The definition also includes "any material used as a component of such a drug," such as component raw materials. *United States* v. *Dianovin Pharmaceutical, Inc.*, 475 F.2d 100 (1973), cert. den. 424 U.S. 830. Provided that products of DNA research are intended for use as a drug product or as a component thereof, and will be introduced into interstate commerce, then they will be subject to the Act's requirements.

The Consumer Product Safety Act, 15 U.S.C. 2051 et seq., is unlikely to have any utility in the regulation of either DNA research or its resulting products. A consumer product must be just that, one intended "for sale to a customer for use in . . . a residence, a school, in recreation . . . or (ii) for personal use, consumption, or enjoyment of a consumer" under the same circumstances. 15 U.S.C. 2052(1). Thus, before any DNA research product is likely to be subject to the provisions of this Act, it very probably will have had to meet more stringent requirements under one or more of the other Acts described in this report.

To conclude, our review of the statutes discussed above suggests that one or more questions need to be asked to determine if the particular DNA research activity, and its products, are subject to regulation under current federal law. One of two threshold requirements must be met in order for the activtity to be subject to any of the laws:

(1) Is the activity federally funded?

(2) Does the activity bear any relationship to interstate or foreign commerce? or is it an entirely private, local endeavor? Do the end products, or components thereof, enter commerce or affect commerce?

Some other, more specific, questions are:

(3) Is the research activity being conducted with a specific identifiable purpose? For what are its products intended?

(4) Does the activity present an "unreasonable risk?"

Even where the research is determined to be subject to one or more federal laws, it will be dependent on the specific nature of the activity involved. Current law, as we indicated at the outset of this report, does not provide for comprehensive regulation of DNA products. If this is to be accomplished additional legislation is necessary.

We hope the information provided is helpful. Should you require additional information or materials please feel free to contact us.

DONNA C. PARRATT, *Legislative Attorney.*

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APPENDIX C

(Re: Civil Action No. 77-0916; Mack v. Califano et al.)

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FILED

FEB 23 1978

JAMES F. DAVEY, Clerk

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR., Plaintiff	)	Civil Action
v	)	No. 77-916
JOSEPH A. CALIFANO, JR., et al., Defendants	)	

FINDINGS OF FACT

1. Plaintiff's complaint, motion for temporary restraining order and preliminary injunction were filed on May 31, 1977.

2. On July 18, 1977 a stipulation was approved by the Court providing that all matters would be stayed pending the finalization of an Environmental Impact Statement (EIS), that defendants would give plaintiff thirty days notice before proceeding with the experiment, and that no such experiment would be conducted prior to the finalization of an EIS.

3. The National Institutes of Health (NIH) guidelines and final EIS were the result of a lengthy administrative process. The scientific community had operated for several years under voluntary restraints limiting the kinds of recombinant DNA research that could be undertaken.

4. A public meeting was held by NIH on February 9th and 10th, 1976 which was announced to the public in the Federal Register. Thereafter NIH published the "decision of the Director, NIH" and NIH guidelines on recombinant DNA research on July 7, 1976. At that time NIH announced that it was preparing a draft environmental impact statement. 41 Fed. Reg. 27902 (1976). On September 9, 1976 the draft EIS was published in its entirety in the Federal Register.

41 Fed. Reg. 38426 (1976). The final EIS was prepared and notice of its availability published in the Federal Register on November 28, 1977. 42 Fed. Reg. 6588 (1977).

5. The NIH guidelines govern all facets of NIH-funded research using recombinant DNA techniques. The guidelines provide detailed requirements for both physical and biological containment designed to insure that recombinant DNA molecules will pose no threat to man or the environment. The experiment is to be conducted in accordance with these guidelines.

6. The laboratory at Fort Detrick is a P4 laboratory with extensive safeguards built into its design. The experiment is to be conducted under P4 physical containment requirements -- the highest level of physical containment. P4 facilities are governed by rules limiting access, providing for change of clothes before entering and leaving, and numerous other safety features. All recombinant DNA materials are handled in gastype safety cabinets and removed only after sterilization.

7. The experiment is to be conducted using EK2 host-vector systems. In the planned experiment, a derivative of E coli K-12 which has been specifically designed to self-destruct if removed from the contolled laboratory environment will be used. E coli K-12 itself is safe and has been used for years without known harm to the laboratory workers or to the environment.

8. E coli K-12 is unable to colonize in the human intestinal tract and causes no known human or animal disease. The EK2 system uses a K-12 derivative that must have special chemicals found only in an artificial laboratory setting in order to survive and is safer than ordinary K-12. If these

chemicals are not present, the EK2 is designed to self-destruct.

9. Recombinant DNA research has already become a valuable aid in progress against illness. Benefits include applied medical advances and an accelerated understanding of the genetic and biochemical basis of the disease process.

10. The experiment is designed to provide important knowledge concerning recombinant DNA technology.

11. The experiment poses no substantial risk to human health or to the environment because (1) there is little likelihood the materials will escape from the maximum containment of the P4 facility; (2) if such an escape did occur, the recombinant DNA molecules would not survive but would self destruct outside the laboratory environment; and (3) the particular virus being used has never been implicated in human disease.

12. Plaintiff has offered no evidence to show that he will suffer irreparable injury or that there is any significant possibility that the experiment will have an adverse impact on the environment.

CONCLUSIONS OF LAW

1. Plaintiff has not shown that he would be irreparably injured unless a preliminary injunction is granted.

2. Plaintiff has not sustained the burdens imposed upon him by Virginia Petroleum Jobbers Association v. FPC

259 F.2d 921 (D.C.Cir. 1958) in that he has failed to demonstrate that he would be irreparably injured in the absence of the issuance of an injunction, that he is likely to prevail upon the merits of the controversy, and that the public interest lies in granting the requested relief.

United States District Judge

Dated: February 23, 1978

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FILED

FEB 23 1978

JAMES F. DAVEY, Clerk

FERDINAND J. MACK, JR., Plaintiff	)	Civil Action No. 77-916
v	)	
JOSEPH A. CALIFANO, JR., et al., Defendants	)	

O P I N I O N

Plaintiff seeks a preliminary injunction to prevent an experiment testing the biological properties of polyoma DNA (deoxyribonucleic acid) cloned in bacterial cells. The experiment is to be conducted in Building 550, Frederick Cancer Research Center at Fort Detrick, Maryland. Also before the Court is defendants' motion to vacate a voluntary stay.

Defendants are Joseph A. Califano, Jr., Secretary of Health, Education, and Welfare, Donald S. Frederickson, Director of National Institutes of Health, and John E. Nutter, Chief Officer of Specialized Research and Facilities, National Institute of Allergies and Infectious Diseases, National Institutes of Health.

On May 31, 1977 plaintiff, an infant resident of Frederick, Maryland, filed a motion for temporary restraining order and preliminary injunction to enjoin defendants from undertaking the experiments or constructing facilities at Fort Detrick to be used for the research. On July 18th a stipulation was entered into by the parties staying all proceedings pending finalization by the defendants of an Environmental Impact Statement and providing for 30 days notice to plaintiff of any experiments to be conducted at

Fort Detrick after such finalization. In accordance with the stipulation, defendants advised plaintiff that an Environmental Impact Statement (EIS) became final on November 28, 1977 when the Council on Environmental Quality published notice of its receipt in the Federal Register. Plaintiff contends that the statement does not comply with the requirements of the National Environmental Policy Act (NEPA), 42 U.S.C. 4322(a)c and other statutes.

A motion of the American Society for Microbiology for leave to file a brief as Amicus Curiae with respect to the public health consequences of the proposed research was granted. Counsel for the Society participated in oral argument and submitted a brief. Dr. Naum S. Bers, Rockville, Maryland, appeared individually as a concerned citizen and was granted permission to file a statement.

Plaintiff asserts that defendants are planning to conduct experiments with polyoma, a virus known to cause cancer in mice. He states that the nature of the organisms to be created by the research is such that even a miniscule quantity, if released, in the environment would represent a threat to life and health. He further contends that the Fort Detrick experiments are to be conducted by defendants without determining the applicability of NEPA and according to the very guidelines of the Department of Health, Education, and Welfare (HEW) classified as "prohibited".

Defendants on the other hand take the position that the EIS and NIH (National Institutes of Health) guidelines reflect the cautious manner in which the scientific community and NIH have considered the new technology involving recombinant DNA molecules. They further state that the final EIS was completed after extensive public comment and discussion of alternatives. Much of plaintiff's concern, they state, is based

on an apparent misunderstanding of the nature of the materials to be used in the experiment. Plaintiff's affidavits are based on the belief that the experiment here in question will be conducted utilizing a common strain of escherichia coli (E coli) as the host-vector for the planned studies. Significantly, the NIH guidelines "prohibit certain kinds of recombinant DNA experiments which include virtually all the known hazards -- for example, those involving known infectious agents."

The research is now restricted by these guidelines to implanting any new genes into enfeebled strains of E coli, a human gut bacteria that has been modified even further to make it safe as the new DNA's laboratory host. In the planned experiment a derivative of E coli K-12, which has been specifically designed to "self destruct", will be employed. E coli K-12 is unable to colonize within the human intestinal tract and causes no known human or animal disease. See EIS at page 73. This EK2 host-vector system will not survive passage through the intestinal tract of animals and will "die" because of its dependency on chemicals not found in nature.

Defendants further point out that the complete experiment will be conducted in P4 physical containment laboratories which have been shown to safely contain microbes presenting a known and demonstrable hazard to man. For each certified EK2 system, "Appendix H, page 10 of the EIS", NIH reviews extensive scientific data to determine that the system meets the standards for safety. EIS at 81. See NIH guidelines, Appendix D, page 15. It is evident, therefore, that there is actually a two step distinction between the common strains of E coli which "do live in people" and the EK2 host-vector system which will be used in these experiments.

Counsel for the American Society for Microbiology states that the weight of scientific opinion now considers that recombinant DNA research in accordance with the NIH guidelines will not have adverse environmental or public health consequences. He contends that the present guidelines are more conservative than necessary and that certain restrictions in these guidelines could be safely modified. He further asserts that these guidelines are not in fact the very guidelines of HEW classified as "prohibited" as was asserted by plaintiffs. In the opinion of the Society, the proposed Fort Detrick experiment will specifically advance the public interest and present no risk of harm to the environment.

The research involves dividing and then rejoining the heredity-carrying material of various organisms - deoxyribonucleic acid, or DNA - to make recombinant hybrids that carry some of the traits of two unrelated forms. It is contended that the value of such work is that it may create new medicines, vaccines, industrial chemicals or crops. The risk, some scientists claim, is that it could create unexpectedly dangerous new ailments or epidemics. Many scientists are of the opinion that exaggerations of the hypothetical hazards have gone far beyond any reasoned assessment. They take the position that the experience of the last four years, including many laboratory experiments, has shown no actual hazards.

Recently the Supreme Court has summarized the limited role of the courts in determining whether the

agencies have complied with NEPA.

> The only role for a court is to insure that the agency has taken a 'hard look' at environmental consequences; it cannot 'interject itself within the area of discretion of the executive as to the choice of the action to be taken'. Kleppe v. Sierra Club, 427 U.S. 390, 410 n. 21 (1976) citing Natural Resources Defense Council v. Morton, 458 F.2d 827, 838, 148 U.S. App. D.C. 5, 16 (1972).

The EIS does represent a "hard look" by NIH at recombinant DNA research performed in accordance with its guidelines. It appears that compliance with the NIH guidelines will insure that no recombinant DNA molecules will escape from the carefully controlled laboratory to the environment.

Plaintiff requested an extension of time to furnish additional evidence. He submitted supplemental affidavits from four of his previous affiants which reaffirmed their previously expressed opinions. None of the affidavits established that the experiment is likely to cause harm to human health or to the environment. The Recombinant DNA Research Guidelines represent an effort by many scientists to evaluate the hazards and provide safe methods for their control. The record reflects that NIH has carefully considered the potential risks of this experiment under the guidelines and has taken the necessary precautions.

The experiment is designed to provide important and needed information on the possibilities of recombinant DNA technology. Important scientific information relative to the possibilities of this technology would be delayed if a preliminary injunction were granted.

Accordingly, plaintiff's motion for a preliminary injunction is denied. Defendants' motion to vacate stay is granted.

John Lewis Smith, Jr.
United States District Judge

Dated: February 23, 1978

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FILED

FEB 23 1978

JAMES F. DAVEY, Clerk

FERDINAND J. MACK, JR., Plaintiff	)	Civil Action
v	)	No. 77-916
JOSEPH A. CALIFANO, JR., et al., Defendants	)	

O R D E R

Upon consideration of plaintiff's motion for preliminary injunction, defendants' memorandum in opposition thereto, the brief of the American Society for Microbiology Amicus Curiae, affidavits, exhibits, supplemental memoranda submitted by the parties, and after oral argument, it is by the Court this 23rd day of February, 1978

ORDERED that plaintiff's motion for preliminary injunction is denied, and it is further

ORDERED that defendants' motion to vacate stay is granted.

United States District Judge

United States Court of Appeals
for the District of Columbia Circuit
FILED FEB 27 1973
GEORGE A. FISHER
CLERK

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. An infant	:	
Appellant	:	No. 78-1156
v	:	
JOSEPH A. CALIFANO, JR. et al	:	
Appellees	:	

ORIGINAL

MOTION TO ENJOIN APPELLEES PENDING APPEAL FROM CONDUCTING RECOMBINANT DNA EXPERIMENTS

1. Appellant, an infant resident of Frederick County, Maryland, sued Appellees below in an attempt to enjoin them from conducting a series of scientific laboratory experiments at Ft. Detrick, Frederick, Maryland, near where he lives. The experiments sought to be enjoined utilize recombinant DNA techniques, and are termed "Risk Assessment Studies." These experiments, to be conducted over a one year period, seek intentionally to create in the laboratory a bio-hazard in order to assess the risk of performing recombinant DNA research. Appellant's claim for relief was based on the failure of the Appellees to prepare an Environmental Impact Statement, as required by NEPA (42 USC § 4331-4347).

2. The DNA technology is succinctly set forth in an editorial in the New England Journal of Medicine:

> "Recombinant DNA technology makes it possible to remove DNA from any organism, to chop the DNA enzymatically into smaller sequences of genes, to splice these genes into an appropriate vector (usually a virus or plasmid), and then to use the vector to infect an animal, plant or bacterial cell of choice. The end result then is the insertion of the foreign genes of interest into a new host. This revolutionary technic permits genetic information to cross species barriers readily. It has allowed genes derived from animal cells and their viruses to be implanted into bacteria, and bacterial genes to be inserted into animal cells. The usual 'time gap' (a potential safety valve) between a fundamental discovery in basic science and its application as a technology disappeared in record time with recombinant DNA studies. With its capacity to rearrange the genetic heritage of millions of years of evolution, this technology appears to offer a power to transform living organisms comparable to the power of nuclear fission to transform matter." N.E.J.M. May 26, 1977.

3. The purpose of the experiments is to attempt to create such bio-hazards, in an effort to quell fears about the research.[1] As set forth in the affidavits of various physicians and scientists filed by Appellant, great harm to this and succeeding generations may result from the Risk Assessment Studies, despite Appellees' attempts to restrict the bio-hazards to the laboratory. This concern is echoed by

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[1] Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules (hereinfater, EIS) Part One page 101.

leading scientists in articles filed in the case below, and again, perhaps the most succinct comment on this point is that from the same editorial in the New England Journal of Medicine:

> "That the NIH is providing millions of dollars for construction of containment facilities for some of this research is to its credit. Yet the 'Fort Detrick Experience' and the records of the Center for Disease Control make it painfully clear that absolute containment of micro-organisms is impossible--even in laboratories where workers are exceedingly well trained and experienced in working with pathogenic organisms. Human frailty will guarantee mistakes. What, then, can be expected from numerous new laboratories recently involved in recombinant DNA research whose personnel have at best had a three-day course on containment procedures? Here, we have the potential for a unique form of pollution, biologic pollution, and it will be distinguished by its irreversibility. In contrast to nuclear-power plants, which can be closed down, micro-organisms will reproduce and perpetuate themselves. They cannot be recalled. Unlike the defined pathogens studied at Fort Detrick, their escape cannot be monitored for." N.E.J.M. May 26, 1977 [3]

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[3] Wedum AG: The Detrick Experience as a guide to the probable efficacy of P4 microbiological containment facilities for studies on microbial recombinant DNA molecules. Recombinant DNA Research (DHEW Publication No. [NIH] 76-1138). Vol. 1. Washington, D.C., Government Printing Office, 1976

4. Subsequent to the filing of the action below, Appellees stipulated that the Risk Assessment Studies would not go forward

without the preparation of an Environmental Impact Statement, which was the primary basis upon which the Appellant sought to have the experiments enjoined in the first place. Appellees later filed an EIS, but one which dealt with the guidelines for Recombinant DNA Research, not one which dealt with the subject experiments, which are designed to attempt to create a bio-hazard.[2] The only reference in the EIS to these experiments is at page 101 of Volume 1, as follows:

> "Virologists of the National Institute of Allergy and Infectious Diseases are preparing to conduct experiments at the Frederick Cancer Research Center, Frederick, Maryland, which should provide data to help determine if recombinant DNA research could result in real hazards."

5. Appellant in this action seeks very limited relief. He does not seek to enjoin general DNA research. Nor does he claim that Risk Assessment Studies--indeed attempts even to create bio-hazards--should not take place. What he claims is that before such risky experiments take place in his backyard, an EIS as to the experiments should be prepared, so all persons will have an opportunity to fully express themselves on the issue, and the real hazards to the health and welfare of Appellant and his community can be ascertained. Appellees

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[2] Biohazard: A contraction of the words "biological hazard"; infectious agents presenting a risk or potential risk to the well-being of man, or other animals, either directly through infection or indirectly through disruption of the environment. National Institutes of Health Environmental Impact Statement Part Two, October 1977, Appendix A-1

have attempted to demonstrate the relatively little likelihood that the organisms will escape-from the laboratory, and that if they do escape, probably will not survive. No consideration has been given to the harm to Appellant, and his environment, if Appellees' attempts in this regard are unsuccessful.

RELIEF SOUGHT

Appellant requests that this Court enjoin Appellees, from conducting at Ft. Detrick, Maryland, proposed experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells, until this Court has had an opportunity to rule on Appellant's appeal from the decision of the United States District Court for the District of Columbia Circuit denying his motion for a preliminary injunction. Counsel for Appellees has advised counsel for Appellant that laboratory preparations will commence on February 27 or 28, and the actual experiments in question will begin in about two weeks. Unless there is continuity in the injunction, the genie may be let out of the bottle, beyond the recall of an order of this, or any other, court.

Ferdinand J. Mack
17 West Jefferson Street
Suite 106
Rockville, Maryland 20850
Attorney for Appellant

CERTIFICATE OF MAILING

I hereby certify that a copy of the foregoing was mailed, postage prepaid this 24 day of Feb, 1978, to Toby Kaczensky, Assistant U.S. Attorney, U.S. District Courthouse, Room 3438-B, Washington, D.C. 20001, Garry Randall, Esquire, Land and Natural Resources Division, Department of Justice, Room 2139, 10th and Constitution, N.W. Washington, D.C. 20530 and William Althen, 1800 M. Street, N.W., Washington, D.C.

Ferdinand J. Mack

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FILED

FEB 23 1978

JAMES F. DAVEY, Clerk

FERDINAND J. MACK, JR.,	)	
	)	
Plaintiff	)	Civil Action
	)	
v	)	No. 77-916
	)	
JOSEPH A. CALIFANO, JR., et al.,	)	
	)	
Defendants	)	

ORDER

Upon consideration of plaintiff's motion for preliminary injunction, defendants' memorandum in opposition thereto, the brief of the American Society for Microbiology Amicus Curiae, affidavits, exhibits, supplemental memoranda submitted by the parties, and after oral argument, it is by the Court this 23rd day of February, 1978

ORDERED that plaintiff's motion for preliminary injunction is denied, and it is further

ORDERED that defendants' motion to vacate stay is granted.

United States District Judge

UNITED STATES COURT OF APPEALS

DISTRICT OF COLUMBIA CIRCUIT

United States Court of Appeals for the District of Columbia Circuit
FILED MAR 3 1978
GEORGE A. FISHER CLERK

No. 78-1156

FERDINARD J. MACK, JR.,

Appellant

v.

JOSEPH A. CALIFANO, JR., ET AL.,

Appellees

OPPOSITION TO MOTION FOR AN INJUNCTION PENDING APPEAL

This case, facially, simply represents an appeal from the denial of a preliminary injunction. The Court is now being asked to rule on a motion for an injunction pending appeal, from the denial of a preliminary injunction. The tests for any such injunctive relief, either in this Court or in the district court are set out and refined in Washington Metropolitan Area, Etc. v. Holiday Tours, _____ U.S.App.D.C. _____, 559 F.2d 841 (1977). The tests may be summarized as follows: (1) Does the petitioner have a serious legal case to present; (2) Will the petitioner be irreparably injured without relief; (3) Will a stay substantially injure others; (4) Where lies the public interest.

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*/ Attachment to Defendants' Memorandum in Opposition to Plaintiff's Motion for a Preliminary Injunction.

In order to answer those questions, this Court, as the district court, will have to examine what is at stake here.

This case is alleged to be a NEPA-based attack upon a single experiment to be performed at Fort Detrick, Maryland. That experiment, however, is designed to develop information which will be used to reassess the federal government's basic guidelines, published by the National Institute of Health (NIH), on recombinant DNA research. Delay in this experiment will delay possible changes in guidelines affecting all recombinant DNA research. (Affidavit of John E. Nutter, copy attached as Appendix A to this opposition.) At stake here is time. The Appellant (Mack) has already delayed this important experiment an additional thirty days by submitting his original evidentiary affidavits with reference to the wrong strains of E. Coli bacteria, ones other than that strain described for use in the experiment, and then obtaining an extension of time to get affidavits with respect to the correct bacteria (Mack's supplementary affidavits; District Court's Opinion p. 5. The Opinion, Findings of Fact, and Conclusions of Law of the District Court are attached as Appendix B to this opposition).

The public interest is in speedy reassessment of these fundamental NIH guidelines. The injury in delay is that

only the federal DNA research program will be delayed. Other DNA research programs will continue, pulling ahead of ours.(EIS pp. 65-67. Four copies of the EIS are being filed with this opposition.) Moreover, our influence with respect to those programs will be lessened. DNA research is an area where guidelines of respectable scientific bodies are examined by one another and given important weight (EIS pp. 15-22). NIH's guidelines were important to researchers not obliged by federal law to follow them.

It can plainly be seen that Mack fails the third and fourth tests of Washington Metropolitan Area, Etc. v. Holiday Tours, supra. We turn next to whether Mack presents a serious case on the merits.

The experiment at issue involves DNA from Polyoma, a virus which can cause tumors in new born mice under laboratory conditions (no tumors have been found in wild mice, though the virus is common in nature)(Appendix A). Polyoma DNA material is to be combined with DNA material from a specially weakened form of E. Coli K-12, a laboratory developed strain of bacteria which cannot live in nature because of its dependence on chemicals found only in the laboratory (Slip Op. p. 3, Findings of Fact p. 2). Use of these specific organisms, extremely unlikely to harm any creature even if the resultant cells should escape from the laboratory, is a form of biological containment (EIS p. 55).

The experiment is also to be performed in the strictest known physical containment laboratory conditions, so as to prevent excape of the results of the experiment (Slip Op. p. 3, Findings of Fact p. 2, EIS p. 51). The combination of physical and biological safeguards to be used are exceptionally strict. The experiment will be conducted in rigorous conformance with the guidelines developed by NIH, and discussed in its programmatic EIS on recombinant DNA research (EIS p. 51-52, 55, 57-61). Mack does not challenge the programmatic EIS. His position is that a separate EIS is needed for this particular experiment.

The programmatic EIS acknowledges the hypothetical risks in all recombinant DNA research (e.g., pp. 1, 23-31, 38), however, any such dangers are unpredictable unknowns, based on current knowledge, and would constitute unexpected results. The remote possibility of spread of harmful microbes is acknowledged, and the impossibility of absolute prediction of results is discussed (EIS pp. 23, 99, et seq.). There is a deliberate election to accept the hypothetical risks because disasterous results are extremely unlikely and great benefits are possible (EIS pp. 4-5, 89-90). The subject experiment is mentioned in the EIS as specifically intended and needed to assist in further analysis of recombinant DNA research (EIS p. 101). The experiment is not only contemplated in the EIS, it is a member of a class of contemplated experiments (EIS p. 82).

Mack objected before the district court that there is no further EIS discussion of the probable result of this experiment -- which experiment is specifically cited in the EIS as an important unknown which has to be resolved. It is plainly unreasonable to demand detailed discussion of possible results in the area which is the specific experimental unknown. Scientists' Institute for Public Information v. AEC, 156 U.S.App.D.C. 395, 409, 481 F.2d 1079, 1093 (1973). Mack also objected that there were no alternative experiments discussed. As far as alternative experiments are concerned, the object is to find out what happens in this particular variety of recombinant DNA experiment, combining a virus, which affects only rodents, producing tumors under laboratory conditions, with a weakened laboratory bred bacteria. The intention is to see if the bacteria with the altered DNA will cause tumors in mice under the same special conditions as the virus caused tumors in mice. There is absolutely no intention to create a "biohazard," as Mack alleges. To the contrary, the district court specifically found that the experiment poses no substantial risk (Finding of Fact No. 11). The information from the experiment is needed to reassess the guidelines. It is difficult to understand how the information can be obtained without doing the experiment. Mack does not suggest that there exists any more suitable virus and bacteria

for this kind of research than the two specially laboratory developed varieties here. Moreover, the EIS specifically discusses why these particular microbes are the preferred experimental mediums, as opposed to all known alternatives (EIS pp. 59, 73, 79). The only real alternative is no research, which is also discussed in the EIS (EIS pp. 66-67). No research is in fact what Mack is seeking by his demand for a separate EIS to discuss the undiscussable. The effect of escape of viable new microbes, demanded in Mack's motion for stay, page 5, was discussed in the programmatic EIS, supra. It is unlikely, yet possible, and the result is unknowable. No separate restatement will change that or provide any additional information. Neither will halting this experiment stop such work, as the EIS notes in its no-action sections, supra. Others will perform these experiments, both here and abroad. Nature performs DNA recombinations all the time and to an unknown extent (EIS pp. 11-12). Mack cannot hope to stop DNA recombination. All he can do is delay the American program. It can therefore be seen that Mack has little or no case to make on the merits.

The district court found both factually, and as a conclusion of law, that Mack had failed the tests of Virginia Petroleum Jobbers Assoc. v. FPC, 104 U.S.App.D.C. 106, 259 F.2d 921 (1958), not showing irreparable injury, likelihood of success on the merits, or that injunction

favors the public interest. The district court found specifically that DNA research was beneficial, that this experiment was important, that the experiment poses no substantial risk, and that Mack showed no evidence of likely injury to himself or the environment (Findings of Fact Nos. 9-12). Mack does not challenge any of those findings, including the one that he failed to show likelihood of injury to himself. 1/

1/ With regard to injury to himself, as well as likelihood of success on the merits, Mack has also totally failed to allege standing, a jurisdictional matter not reached by the district court. Mack's only allegation of harm is that he lives six miles from Fort Detrick and might be injured by release of a dangerous microbe. That is only a general allegation of harm, common to the entire population of the world (spread of disease knows no boundaries, and six miles is no less a barrier than 1,000 miles). Mack has no standing to bring this suit. Metcalf v. National Petroleum Council, ____ U.S.App.D.C. ____, 553 F.2d 176, 186-187 (1977). In Metcalf, plaintiffs alleged that the actions of the National Petroleum Council would cause them to pay higher prices, deny them the lower costs and benefits of alternate energy sources, do general environmental damage, and threaten to pollute, via oil spills, certain specific waterfront lands owned or used by plaintiffs. The court of appeals found no standing, both because the feared injuries were speculative, and because they were not sufficiently individualized:

> It could be argued that an oil spillage is inevitable in areas where the appellants might live on vacation; still, any personal injury which such an occurrence may inflict on appellants is speculative and remote, not real and immediate. The mere occurrence of the type of environmental dangers and risks which concern appellants does not necessarily mean that appellants will suffer a particularized, injurious impact as a result.
>
> * * * * *

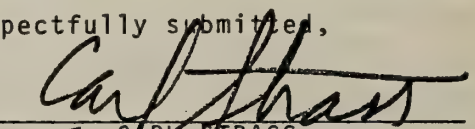
footnote cont'd on next page

Mack fails each of the Holiday Tours tests. Finally, we note that Mack has also failed to satisfy Rule 8(a) F.R.A.P. because he did not initially seek a stay or injunction pending appeal from the district court.

CONCLUSION

For the foregoing reasons the motion for injunction pending appeal should be denied.

Respectfully submitted,



CARL STRASS
Attorney, Department of Justice
Washington, D. C. 20530

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footnote 1/ cont'd from previous page

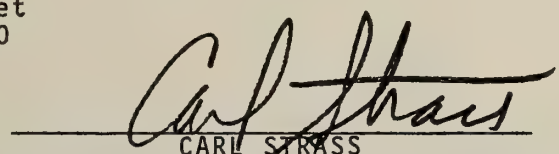
> The appellants asserted injuries with respect to higher petroleum prices, the unavailability of alternative energy sources, and aesthetic blight, if they were to occur, would likely be of the type "held in common by all members of the public" and thus insufficient as a basis for standing. The fact that many are injured does not, of course, preclude an individual party from being granted standing. That individual party must, however, be able to allege and prove "a distinct and palpable injury to himself" as the threshold requirement for standing. Appellants have not shown that they would be able to do this with respect to these injuries. [Footnotes omitted.]

See also Harrington v. Bush, _____ U.S.App.D.C. _____, 553 F.2d 190 (1977). Mack's single standing allegation is even weaker than the allegations found insufficient in Metcalf.

CERTIFICATE OF SERVICE

I certify that a copy of the foregoing Opposition to Motion for an Injunction Pending Appeal has been served upon counsel, by placing same in the United States mail, postage prepaid, properly addressed, this 3rd day of March, 1978, to:

Ferdinand J. Mack, Esquire
Suite 106
Old Town Center
West Jefferson Street
Rockville, Md. 20850



CARL STRASS
Attorney, Department of Justice
Washington, D. C. 20530

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 78-1156 **September Term, 19**

Ferdinand J. Mack, Jr., By and through his mother and next friend, Mildred A. Mack,
Appellant

v.

Joseph A. Califano, Jr. Secretary, United States Department of Health Education and Welfare et al.

Civil Action No. 77-0916

United States Court of Appeals
for the District of Columbia Circuit

FILED MAR 8 1978

GEORGE A. FISHER
CLERK

BEFORE: Fahy, Senior Circuit Judge; and MacKinnon, Circuit Judge

O R D E R

On consideration of appellant's motion to enjoin appellees pending appeal from conducting recombinant DNA Experiments, and of the opposition thereto, and of the record on appeal herein, it is

ORDERED by the Court that appellant's aforesaid motion is denied, and it is

FURTHER ORDERED by the Court, sua sponte, that the order by the District Court on appeal herein be, and the same hereby is, affirmed.

Per Curiam

C.J.

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR.,
an infant :

Route 2
Frederick, Maryland 21701 :

BY AND THROUGH HIS MOTHER :
AND NEXT FRIEND,
MILDRED A. MACK, :
Route 2
Frederick, Maryland 21701, :

Plaintiff :

v. :

JOSEPH A. CALIFANO, JR., :
Secretary,
United States Department of :
Health, Education and Welfare
330 Independence Avenue, S.W. :
Washington, D.C., :

and

DR. DONALD S. FREDERICKSON :
Director
National Institutes of Health :
9000 Rockville Pike
Bethesda, Maryland, :

and :

JOHN E. NUTTER,
Special Assistant to the :
Deputy Director
Department of Allergy and :
Infectious Diseases
National Institutes of Health :
9000 Rockville Pike
Bethesda, Maryland, :

Defendants :

77- 0916

Civil Action No._____

SMITH, J.

FILED

MAY 31 1977

JAMES F. DAVEY, Clerk

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

1. Plaintiff is an infant, a citizen of the United States, and a resident of Frederick County, Maryland. Defendants are the Secretary, and employees, of the United States Department of Health, Education and Welfare, a branch of the Executive Department of the United States Government and are sued in their official capacities. Jurisdiction is founded upon 28 U.S.C. §1331 (Federal Question), 28 U.S.C. §2201-2202 (Declaratory

Judgments), 28 U.S.C. §1361 (Mandamus), 42 U.S.C. §4331-4347 (NEPA) and 38 Federal Regulations 10859 (Guidelines For Preparation of Environmental Impact Statements, Council on Environmental Quality, May, 1973).

2. There is located within Frederick County, Maryland, approximately 6 miles from the residence of plaintiff, a federal reservation known as Ft. Detrick. By virtue of the proximity of Ft. Detrick to plaintiff's residence, the food and water which he consumes, the air he breathes, and the area in which he plays and lives are subject to contamination by activities carried on at Ft. Detrick.

3. Defendant Califano, as Secretary of the United States Department of Health, Education and Welfare, is charged with the administration of that agency, and is the ultimate superior of defendants Frederickson and Nutter. Defendant Frederickson is the Director of the National Institutes of Health, and the superior of defendant Nutter. Defendant Nutter has been assigned by Frederickson the job of NIH Project Manager for the establishment of "P-4" research facilities at Ft. Detrick, where,Nutter has stated, biohazard assessment experiments in Recombinant DNA Research will commence beginning about June 1, 1977.

4. In about 1973, a scientific technique was developed which enabled scientists to propagate novel living organisms by combining the hereditary substance, DNA from unrelated organisms. This technique has been variously termed recombinant DNA research, gene splicing, gene stitching, molecular cloning, and genetic manipulation, among others.

5. DNA, or deoxyribonuleic acid, is the chemical substance which makes up the genes and chromosomes of living organisms. It contains the code or set of instructions which guides the development, maintenance and reproduction of organisms and determines their form.

6. With the use of enzymes called restriction enzymes, or endonucleases, it is possible to cleave the DNA of one organism and splice in a portion of the DNA of a second

organism which has been similarly cleaved. The splicing can be sealed with another enzyme called DNA ligase, and the composite DNA can then be inserted into a host organism where the foreign genetic information may be expressed and reproduced.

7. Using recombinant DNA techniques, genetic information from any living organism can be implanted into bacteria. Also, genetic information from lower organisms such as viruses can be inserted into and expressed in higher organisms. This rapid exchange of genetic information across wide species barriers, as can occur in recombinant DNA research, is rare in nature and limited by reproductive barriers.

8. The recombinant DNA technique is a powerful new scientific tool which, while providing speed and convenience in the conduct of genetic research, permits hitherto impossible genetic manipulations with little control over the outcome of these manipulations. It is now possible artifically to manipulate the course of evolution within a short period of time using a technique different and far more extensive than that of traditional breeding techniques. Recombinant DNA research raises unprecedented hazards to humans and the environment compounded by the inability to predict the outcome of the research, and the ability of a dangerous organism to replicate, maintain and establish itself in the ecosphere.

9. Escherichia coli (E. coli), the host organism most widely used in recombinant DNA research, is a ubiquitous organism which resides in the human gut, in all warm blooded species, economically important and otherwise, in water supplies, and other places. It has pathogenic, or disease causing capabilities. E. coli is frequently associated with upper urinary tract infections in humans. It is capable of transferring the foreign DNA implanted in it to other microorganisms, which could result in the formation of a novel pathogen.

10. Defendant, Nutter, acting at the instructions of defendants Califano and Frederickson, and using Federal funds provided by defendant Califano, is causing Building 550 at Ft. Detrick, to be renovated, and defendants are presently in the

process of certifying and training a staff to operate a laboratory in that building with the intention, by June 1, 1977, of conducting Recombinant DNA research in Building 550, as set forth in a Protocol entitled "Proposed Experiments on The Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells," (The "Protocol") a copy of which is annexed hereto and designated Exhibit No. 1.

11. Section 102(2)(C) of NEPA, 42 U.S.C. 4322(2)(C) provides that all agencies of the Federal Government shall:

> (C) Include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on -
>
> (i) the environmental impact of the proposed action,
>
> (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,
>
> (iii) alternatives to the proposed action,
>
> (iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and
>
> (v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented. Prior to making any detailed statement, the responsible Federal official shall consult with and obtain the comments of any Federal agency which has jurisdiction

> by law or special expertise with respect to any environmental impact involved. Copies of such statement and the comments and views of the appropriate Federal, State, and local agencies, which are authorized to develop and enforce environmental standards, shall be made available to the President, the Council on Environmental Quality and to the public as provided by Section 552 of Title 5, United States Code, and shall accompany the proposal through the existing agency review processes....

12. Defendant, Califano, in his testimony before the Subcommittee on Health and Scientific Research, Committee on Human Resources, United States Senate, on April 6, 1977, testified:

> "But while the new research techniques /Recombinant DNA/ holds the promise of significant scientific advances, they also pose risks of uncertain magnitude. For example, Recombinant DNA in a microorganism may alter it in unpredictable, and possibly undersirable ways. Should the altered microorganism escape from a laboratory, it might cause disease or modify the environment...."
>
> "At the present time, it is extremely difficult to assess accurately the nature of the hazards posed by Recombinant DNA research. More precise assessment of the risks must await further inquiry."

13. Defendant Nutter has admitted publicly that Recombinant DNA Research at Ft. Detrick, as proposed, carries with it the potential for serious risks to the environment and

the people living in Frederick County, Maryland, including plaintiff.

14. The present state of the science is not substantially progressed past that which existed at the time Dr. Robert Sinsheimer, Chairman of the Division of Biology, California Institute of Technology at Pasadena, California, wrote in "New Scientists", on October 16, 1975:

> "Briefly, it became apparent to the scientists involved at almost the last hour when all of the techniques were really at hand that they were about to create novel forms of self-propagating organisms,derivatives of strains known to be normal components of the human intestine flora with almost completely unknown potential for biological havoc. Could an Escherichia coli strain carrying all or part of an oncogenic /cancer causing/ virus become resident in the human intestine? Could it thereby become a possible source of malignancy? Could such a strain spread throughout a human population? What would be the consequences if even an insulin secreting strain became an intestinal resident? Not to mention the more malign or just plain stupid scenarios such as those which depict the insertion of the gene for botulinus toxin into Escherichia coli.
>
> "Unfortunately the answers to these questions in terms of probabilities that some of these strains could persist in the intestines, the probabilities that the modified plasmids might be transferred to other strains, better adapted to intestinal life, the probabilities that the genome of an oncogenic virus could escape, could be taken up, could transform a host cell, are all largely unknown."

15. The experiments which the defendants intend to conduct at Ft. Detrick includes the use of Polyoma, a virus which

is known to cause cancer in mice. Whether that cancer virus will cause cancer in human beings is unknown. The nature of the organisms to be created by the research at Ft. Detrick, is such that, if released from containment, they may remain dormant in the environment for a substantial period of time, and continue to possess the potential for infecting the environment. The organisms may not cause cancer symptoms for 20 to 30 years, and then create illnesses, the treatment of which is not known. These organisms are alive, self-perpetuating and reproduce rapidly. Conduct of such experiments at Ft. Detrick exposes large segments of population to many unpredictable health hazards. Even a miniscule quantity of the organisms to be created, if released in the environment, due to their ability to reproduce rapidly, represents a real threat to life and health which is beyond the present knowledge of science to cope with.

16. Despite the requirements of Section 102(2)(C) of NEPA, defendants have, in connection with the proposed Ft. Detrick experiments, and the renovation of the laboratory there, failed to prepare the Environmental Impact Statement required by that statute, and have failed to comply with the requirements of the guidelines promulgated by the Council on Environmental Quality as to statements on proposed Federal actions affecting the environment (38 Fed. Reg. 10859, May, 1973), and have otherwise violated Federal statutes, and regulations.

17. Unless the actions of defendants are enjoined,

plaintiff, the environment in which he lives, and his fellow residents of Frederick County, Maryland, if not the entire United States, will suffer permanent and irreparable injury for which there is no adequate remedy at law.

WHEREFORE, plaintiff demands:

1. That this Court enter a judgment declaring that the actions of defendants taken in connection with the experiments in Recombinant DNA Research to be performed at Ft. Detrick, Maryland, are unlawful;

2. That the defendants be enjoined preliminary and permanently, from conducting experiments at Ft. Detrick, Maryland, on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells;

3. That the defendants be enjoined, preliminary and permanently, from entering into or permitting performance of contracts for the construction or renovation of facilities to be used for the conduct of Recombinant DNA Research at Ft. Detrick, Maryland;

4. That the defendants be enjoined, preliminary and permanently, from constructing or renovating facilities at Ft. Detrick, Maryland to be used for the conduct of Recombinant DNA Research.

5. That this Court enter a judgment declaring that the defendants are required by §102(2)(C) of NEPA to prepare and circulate for comment a final environmental impact statement

with respect to the proposed experiments to be conducted at Ft. Detrick, Maryland, on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells.

6. That this Court enter a temporary restraining order, restraining defendants from the actions set forth in Paragraphs 2.-4. above.

7. And, for such other and further relief as to the Court seems met and proper.

FERDINAND J. MACK
17 West Jefferson Street
Rockville, Maryland 20850
279-2230

Attorney for Plaintiff

I swear that I verily believe
the facts stated in this pleading
to be true.

Mildred A. Mack
Mother and Next Friend of
FERDINAND J. MACK,JR.,
an infant.

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR.,
an infant
Route 2
Frederick, Maryland 21701
BY AND THROUGH HIS MOTHER
AND NEXT FRIEND,
MILDRED A. MACK,
Route 2
Frederick, Maryland 21701,

Plaintiff

v.

Civil Action No. 77- 0916

JOSEPH A. CALIFANO, JR.,
Secretary,
United States Department of
Health, Education and Welfare
330 Independence Avenue, S.W.
Washington, D.C.,

and

DR. DONALD S. FREDERICKSON
Director,
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland,

and

JOHN E. NUTTER,
Special Assistant to the
Deputy Director
Department of Allergy and
Infectious Diseases
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland,

Defendants

FILED
MAY 31 1977
JAMES F. DAVEY, Clerk

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF
MOTION FOR TEMPORARY RESTRAINING ORDER
AND PRELIMINARY INJUNCTION

1. This Motion does not seek to restrain activity in the field of gene research. It asks only that before plaintiff

is exposed to the dangers of this new research the requirements of the National Environmental Protection Act and other laws of the land be complied with.

2. This area of scientific research has perhaps the most far reaching potential for harm to the inhabitants of the earth that has yet been encountered. Only the uncertainties that existed at the detonation of the first nuclear and thermonuclear devices, comes close to the scientific controversy which surrounds the issue of recombinant DNA research. Highly trained, well motivated and concerned citizens, even Nobel prize winners, are arrayed on both sides of the controversy. The scientific details are fully set forth in the annexed exhibits, and the affidavits in support of this Motion. In simple terms, what confronts the Court is this.

3. Historically, when science has wanted to alter or refine creations of nature to suit human needs and desires, it has been required to do so by imitating nature. Just as the artic fox, by the process of natural selection, developed a white coat for protection in his environment, so science has been able to cultivate fatter cattle, and better corn, and more beautiful flowers by selectively breeding to obtain the desired traits. Such processes, of course, have taken long periods of time, requiring birth of the species involved, growth to maturity, and selective reproduction. By the same token, science has had no success in crossing reproduction barriers laid down by nature which prevented the creation of life across certain prohibited

lines, i. e., high and low life, apples and oranges, humans and other primates, etc.. Recombinant DNA research is expected to change all this.

4. This scientific tool is expected to make it possible, for example, to take genes from cattle with certain desirable traits and combine them with the genes of other cattle, and to produce in a single generation cattle having the traits of both. As in the proposed experiments at Ft. Detrick, barriers between living organisms in nature that could never combine in reproduction are skirted by the laboratory mixing of genes of the two. The Ft. Detrick experiments will involve an attempt to combine genes from viruses that are known to cause cancer in mice (polyoma) with a microorganism that is known to be pathogenic in man (E. coli), and which lives in the intestines of man and all other warm blooded animals. (Protocol, Exhibit No. 1) In nature such a combination could not occur. These new organisms are to be created in laboratories as secure as can be made, as indeed they must; for if they were to be released into the environment, the organisms, which are alive and will continue to grow, may cause disease and maladies never before experienced by man, and may take a generation or more to make themselves known. Little can be added to the potential hazards to plaintiff, (and all who live) as described in the three (3) affidavits filed in support of this Motion. While no one, including the defendants, can predict with certainty what will happen if the organisms are released into the environment, widespread death and disease are distinct possibilities.

5. Frederickson, because of the potential escape of hazardous organisms in DNA research, promulgated "guidelines" for the conduct of such experiments. 41 Fed. Reg. 38427, Sept. 9, 1976. By later preparing a "Draft Environmental Impact Statement" to cover the guidelines, which in turn govern the Ft. Detrick experiments, it would appear that the defendants are estopped to deny the Ft. Detrick experiments require an Environmental Impact Statement. Environmental Defense Fund v. Corps. of Engineers, 325 F. Supp. 728, (E. D. Ark. 1970-71), 325 --F. Supp. 749, (E. D. Ark.), 342 F. Supp. 1211, (E. D. Ark.), aff'd, 470 F.2d 289, (8th Cir. 1972). Sierra Club v. Hardin, 325 F. Supp. 99, (D. Alas. 1971).

6. Frederickson has further committed himself to the view that an environmental impact assessment of the Ft. Detrick experiments is required. In his "Decision of the Director, NIH, to Release Guidelines for research on recombinant DNA Molecules". 41 Fed. Reg. 27902, July 7, 1976, Frederickson states:

> A number of commentators urged NIH to consider preparing an environmental impact statement on recombinant DNA research activity. They evoked the possibility that organisms containing recombinant DNA molecules might escape and affect the environment in potentially harmful ways.
>
> I am in full agreement that the potentially harmful effects of this research on the environment should be assessed. As discussed throughout this paper, the guidelines are premised on physical and biological containment to prevent the release

> or propagation of DNA recombinants outside the laboratory. Deliberate release of organisms into the environment is prohibited. In my view, the stipulated physical and biological containment ensures that this research will proceed with a high degree of safety and precaution. But I recognize the legitimate concern of those urging that an environmental impact assessment be done. In view of this concern and ensuing public debate. I have reviewed the appropriateness of such an assessment and have directed that one be undertaken.
>
> The purpose of this assessment will be to review the environmental effects, if any, of research that may be conducted under the guidelines. The assessment will provide further opportunity for all concerned to address the potential benefits and hazards of this most important research activity. I expect a draft of the environmental impact statement should be completed by September 1 for comment by the scientific community, Federal and State agencies, and general public.

6. Despite all the foregoing, the Ft. Detrick research is to be conducted by defendants without their either determining the inapplicability of NEPA (as required by the Department of Health, Education and Welfare, General Administration Manual ((GAM)) Part 30), or preparing an Environmental Impact Statement (as required by NEPA and the Council on Environmental Quality Guidelines, 38 Fed. Reg. 20550, 40 C.F.R. Part 1500).

7. More startling, the Ft. Detrick experiments are by the very guidelines of HEW classed as "prohibited", for the

following reasons:

A. The National Cancer Institute (a Division of HEW) has established Safety Standards for Research Involving Recombinant DNA, which classify as "moderate risk" the following experiments:

> A genetic recombinant between an animal oncogenic virus and microorganism infectious for man shall be considered moderate risk until its potential for man is determined.

B. Polyoma is an oncogenic (cancer causing) virus of mice (an animal), and in the protocol under attack, will be genetically be combined with E. coli: (a microorganism infectious for man), and thus is by the applicable safety standards of HEW, a "moderate risk" experiment.

C. Defendants' "guidelines" for the carrying out of recombinant DNA experiments provide:

> A. Experiments that are not to be performed. We recognize that it can be argued that certain of the recombinants placed in this category could be adequately contained at this time. Nonetheless, our estimates of the possible dangers that may ensue if that containment fails are such mágnitude that we consider it the wisest policy to at least defer experiments on these recombinant DNAs until there is more information to accurately assess that danger and to allow the construction of more effective biological barriers. In this respect, these guidelines

> are more stringent than those initially recomended.
>
> The following experiments are not to be initiated at the present time: ...oncogenic viruses classified by NCI as moderate risk.... (Emphasis added.)

8. While it is true that Congress did not intend NEPA to require impact statements to be prepared each time an agency proposes trival action, it certainly did not intend to exclude all but the largest and most important actions from compliance. The Courts have tended toward the widest scope of application of the statute,the most frequently given reason being that Congress intended NEPA to apply to all Federal Agencies and at the "lowest levels, ... most decisions are formulated and even finalized." 115 Cong. Rec. S. 12117 (Daily Ed. October 8, 1969) (Remarks of Mr. Church, Senate Conferee on NEPA.)

9. The Courts have accepted the view that Congress intended NEPA's various requirements to be interpreted and applied in the strictest manner. The phrase, "to the fullest extent possible," has become the touch stone of NEPA interpretation. The key language is contained in the opening words of §102

> "The Congress authorizes and directs that, to the fullest extent possible:
>
> 1. The policies, regulations, public laws of the United States shall be interpreted and administered in accordance with the policies set forth in this Act, and

> 2. all agencies of the Federal Governement shall ... /comply with the eight action-forcing provisions/ (Emphasis added.)

10. The requirement of compliance "to the fullest extent possible" has been applied with special vigor to the provisions of §§102(2) after the forceful interpretation given to the phrase in Calvert Cliffs' Coordinating Committee v. Atomic Energy Commission, 449 Fed. 2d. 1109 (D.C. Circuit 1971), Cert. denied, 404 U.S. 942 (1972)."

11. It might be argued that this initial step of experimentation at Ft. Detrick is a relatively minor action and, consequently, not of sufficient magnitude to justify requirement that an environmental impact statement be prepared. Such an argument overlooks the broader aspect of what is involved, namely that this experiment is admittedly but the first stepping stone towards greater utilization of Ft. Detrick, for recombinant DNA research; it is, as the Court stated, in United States v. 247.37 Acres of Land,/ "but a small cog in anoverall big plan," having major environmental consequences. _____ Fed. Supp. _____, (Southern District Ohio 1971, _____ Fed. Supp. _____, (S. D. Ohio 1972).

12. The admissions of the defendants, their actions acknowledging the serious potential environmental effect, consequent to the research to be conducted, the affidavits of three highly qualified scientists and the controversary reflected in the exhibits filed with this Memorandum clearly demonstrate

that the potential for significantly affecting the quality of the human environment by the Ft. Detrick experiments exists. Plaintiff suggests that such a state of affairs is all that must be demonstrated to the Court in order to order the defendants to prepare an Environmental Impact Statement. In Citizens for Reid State Park v. Laird, 336 Fed. Supp. 783, 788, the Court stated:

> "NEPA... require(s) all Federal agencies to incorporate as an integral part of their planning process consideration of the environmental consequences of any proposed action, and wherever such consideration indicates that the action may significantly affect the quality of the human environment to prepare and file a detailed impact statement. (Emphasis added.)

13. Our Court of Appeals has likewise found that "major Federal action" is to be judged by the magnitude of the potential environmental consequences:

> "The introduction of 'stretch' jets into /Washington National Airport/ ... in 1968, was not a "major action" as that term is used in §102(2)(C). It bases this conclusion on its findings that the difference between the 727-200 (stretch jet) and the 727-100 (stretch yet's predecessor) is minimal insofaras "affecting the quality of human environment" is concerned.

14. Further support is found in Izaak Walton League v. Schlesinger, 337 Fed. Supp. 287, where this Court, in considering

whether "major Federal action" was involved in the licensing of a nuclear power station, focused upon the evidence which indicated that the environment might be significantly affected.

15. In looking to other sources of statutory support, plaintiff would point to §5~~(b)~~ 1500.6 of the Guidelines of the Council on Environmental Quality, which provides:

> "The statutory clause 'major Federal actions significantly affecting the quality of human environment' is to be construed by agencies with a view to the overall, cumulative impact of the proposed action (and of further actions contemplated). Such actions may be localized in their impact, but if there is potential that the environment may be significantly affected, the statement is to be prepared. Proposed actions, the environmental impact of which is likely to be highly controversal, should be covered in all cases."

16. Plaintiff seeks the extraordinary remedy of injunction authorized by Rule 65, F. R. Civ. P. To be put on the scales in balancing the equities of plaintiff and defendants, is the horrendous potential of harm which may result from the experiments if they go forward. Balanced against that, is the delay necessary for the preparation by the defendants of an environmental impact statement. At the risk of oversimplifying the issue, the plaintiff would inquire, whether civilization, having survived this far without the tool of recombinant DNA research, will suffer substantial harm if it is denied science a few more months.

17. While plaintiff recognizes the extraordinary nature of the relief sought, he contends that he has in this action under NEPA, a "special claim to judicial protection". Environmental Defense Fund v. Ruckelshaus, 439 Fed. 2d. 584, 598 (D.C. Circuit 1971).

18. Finally, plaintiff would call to the attention of this Court, the opinion of our Court of Appeals in Jones v. District of Columbia Redevelopment Land Agency, 499 Fed. 2d. 502, 512 (D.C. Circuit 1974), where the Court stated:

> "The harm against which NEPA's impact statement requirement was directed was not solely or even primarily adverse consequences to the environment; such consequences may ensue despite the fullest compliance. Rather NEPA was intended to ensure that decisions about federal actions would be made only after responsible decision-makers had fully adverted to the environmental consequences of the actions and had decided that the public benefits flowing from the actions outweighed their environmental costs. Thus the harm with which courts must be concerned in NEPA cases is not strictly speaking, harm to the environment, but rather the failure of decision-makers to take environmental factors into account in the way that NEPA mandates. And for the purposes of deciding whether equitable relief is appropriate, we think that this harm matures simultaneously with NEPA's requirements, i. e., at the time the agency is, under NEPA obliged to file the impact statement and fails to do so.

CONCLUSION

While this action is brought on behalf of a single infant, the decision of this Court in this case will affect the lives and health of persons throughout this area, if not the world. As lawyers, we sometimes become carried away with rhetoric, and tend to make legal mountains out of common sense mole hills. It would appear difficult, however, to overstate the ramifications of the actions of the defendants that plaintiff seeks to enjoin.

Respectfully submitted:

Ferdinand J. Mack

FERDINAND J. MACK
17 West Jefferson Street
Rockville, Maryland 20850
279-2230

Attorney for Plaintiff

TABLE OF AUTHORITIES

CASES

* Calvert Cliffs' Coordinating Committee v. Atomic Energy Commission, 449 Fed. 2d. 1109 (D.C. Circuit 1971), Cert. denied, 404 U.S. 942 (1972).

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Environmental Defense Fund v. Ruckelshaus, 439 Fed. 2d 584, 598 (D.C. Circuit 1971).

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Izaak Walton League v. Schlesinger, 337 Fed. Supp. 287.

Sierra Club v. Hardin, 325 F. Supp. 99, (D. Alas. 1971).

STATUTES

42 U.S.C. §§4331-4347 (NEPA).

RULES

Rule 65, F. R. Civ. P.

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* - Cases principally relied upon.

OTHER

115 Cong. Rec. S. 12117 (Daily Ed. October 8, 1969)
(Remarks of Mr. Church, Senate Conferee on NEPA.)

Department of Health, Education and Welfare,
General Administration Manual ((GAM)) Part 30).

Council on Environmental Quality Guidelines,
38 Fed. Reg. 20550, 40 C.F.R. Part 1500).

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR., an infant,

Plaintiff :

v. : Civil Action No. 77- 0916

JOSEPH A. CALIFANO, JR., ET AL.,

Defendants :

FILED

MAY 31 1977

JAMES F. DAVEY, Clerk

AFFIDAVIT IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER

1. I, Stephen Havas, am a physician, an Assistant in Medicine at Massachusetts General Hospital, an Instructor in Medicine at Harvard Medical School, and Board Certified in Internal Medicine.

2. I have read and am familiar with a document entitled Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells, by Martin and Rowe (the "Protocol"), for the conduct of experiments in Building 550 at Ft. Detrick, Maryland.

3. These experiments involve the use of polyoma virus, which is known to cause cancer in mice and other rodents. The experiments also employ the bacterium, E. coli, which lives on land and in water all over the earth, and in particular is a common

inhabitant of the large intestine of all warm blooded animals, including humans. Some strains of E. coli are known to cause diarrhea, urinary tract infections and other diseases. In the experiments the DNA (i.e., all the genetic information, including the tumor producing genes) of the above described polyoma virus will be spliced onto a bacterial virus (called lambda phage) or a plasmid, which is a self-replicating piece of DNA, akin to a virus. The plasmid or phage containing the polyoma tumor virus genes will then be inserted into E. coli, where it will be replicated. Whether an E. coli bacterium that contains the genetic information for polyoma tumor virus production will cause cancer in humans or other warm blooded animals, or what kinds of cancers it will cause, what their symptoms will be, how they can be treated, or anything else about the nature of this new organism is unknown. Such an organism is not known to exist in nature.

4. Although precautions may be devised against the escape of the newly created organisms, we know from past experience that human error is unavoidable, and the consequences of escape into the atmosphere of the newly created organism may occur. Because of their novelty, the effect upon the environment of the new organisms and the symptoms of their action upon the environment can not be known in advance. The nature of the organisms to be created by this research is such that, if released from containment, they may remain dormant in the environment for a substantial period of time, and continue to possess the potential for infecting the environment. In addition, the natures of the organisms are likely to be such that

it would be only after a substantial amount of the population is infected that the trouble could be traced to these organisms, and by this time the infection can have spread far and wide. This is due in part to the fact that the organisms may evoke symptoms that are new, may take 20 to 30 years to cause cancer symptoms, or may imitate other diseases. Also unknown are the methods of treatment of any illnesses caused by the new organisms.

5. The greatest danger of these experiments is that the hazard is alive, self-perpetuating, and reproduces rapidly. Once out, it can not be recalled. If released into polluted waters, such as the Potomac River, even relatively small quantities of organisms can rapidly multiply to the point where large populations are threatened. Conduct of such experiments in laboratories contiguous to a large populated area, upstream from a water supply source already reputed to be polluted, unnecessarily exposes the population to many unpredictable health hazards.

6. The E. coli to be utilized in the experiments is a "weakened" strain, as opposed to the natural, "wild type" strain. It is not known whether the weakened strain, when combined with the mouse cancer genes can exchange genetic information with other, wild type strains, but such exchanges occur commonly among different E. coli strains and among E. coli and other microorganisms. The wild type strains of E. coli inhabit the whole environment, living in soil, water and all warm blooded animals, and are carried by insects and fish. If such genetic interchange did occur, there is

absolutely no way of predicting what segment of the environment polyoma virus that has been mixed into a wild type E. coli will infect. However, this possibility clearly poses a threat to all warm blooded animals and indeed to the entire environment.

7. It has been asserted that the "weakened" bacteria used as gene implantation recipients in the experiments have an outside survival probability of one in one hundred million. However, a one quart (reasonable daily working quantity) of laboratory culture of recombinant DNA, the product of the gene splicing experiments, easily contains 10-100 million bacteria. Even a miniscule quantity of harmful organisms in the environment, due to their ability to reproduce rapidly, represents a real danger. The possibilities of grave and unknown risks of the spread of cancer, of slow viruses, or of novel pathogens can not be discounted. Such agents could well become widely disseminated before their noxious effects became evident.

8. The experiments proceed on the assumption, stated as a fact, that polyoma virus only infects rodents and is not a human cancer virus. However, research sufficient to establish the truth of that statement has not been conducted. Polyoma virus was first discovered in 1960, and to date no scientific study has been published as to the incidence of cancer among the laboratory workers who have worked with polyoma over those 17 years. And 17 years since exposure t · a carcinogen is not an overly long induction period for cancer. To say that polyoma is not a human cancer violates fundamental,

accepted, scientific practice, due to the present state of knowledge (or ignorance) of the virus and of cancer epidemiology. However, even if the premise were correct, since the E. coli with which cancer virus is to be combined is known to live in people, there is no way of knowing in advance if the combination of the two will result in an organism capable of causing cancer in humans.

9. The protocol states that the National Institutes of Health intends to make "inactivated bacterial lysates available to interested investigators." This means that the E. coli cells containing the polyoma cancer genes will be burst open (lysed) and will no longer be able to reproduce by themselves. Yet the genetic information is still active within such lysates and can be transferred to other living cells in which it can then reproduce. The protocol implies that the lysates will not be provided P-4 containment--the highest form of safety--and will not be subject to the safeguards that exist at earlier stages in the genetic combination research. Such lysates present at least as much of a hazard as the recombinant E. coli, which are afforded P-4 treatment, in that they can be dispersed in dust and air, and because the inactivated lysate is able to infect other E. coli, or might be taken up by the cells of the investigator. A real threat to the contamination of the environment exists under this portion of the protocol.

Stephen Hamer

STATE OF MASSACHUSETTS)
) ss.
COUNTY OF NORFOLK)

Personally appeared before me, the undersigned, a Notary Public in and for the State and County aforesaid Stephen Hawks, who made oath in due form of law that the foregoing affidavit is true.

WITNESS my hand and notarial seal this 18TH day of MAY, 1977.

Albert J. DeLeconio Jr.
Notary Public

Notary Public in and for the State of Massachusetts, County of Norfolk

ALBERT J. DELECONIO, JR. NOTARY PUBLIC COMMONWEALTH OF MASSACHUSETTS MY COMMISSION EXPIRES MARCH 21, 1981

My Commission expires
March 21st 1981

JNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR., an infant,

Plaintiff

v. Civil Action No. 77- 0916

JOSEPH A. CALIFANO, JR., ET AL.,

Defendants

FILED

MAY 31 1977

JAMES F. DAVEY, Clerk

AFFIDAVIT IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER

1. I, Ruth Hubbard, am a Ph. D., a research associate and lecturer at Harvard University, and have been a Professor of Biology at Harvard University for 3 years.

2. I have read and am familiar with a document entitled Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells, by Martin and Rowe (the "Protocol"), for the conduct of experiments in Building 550 at Ft. Detrick, Maryland.

3. These experiments involve the use of polyoma virus, which is known to cause cancer in mice and other rodents. The experiments also employ the bacterium, E. coli, which lives on land and in water all over the earth, and in particular is a common inhabitant of the large intestine of all warm blooded animals, including humans. Some strains of E. coli are known to cause diarrhea, urinary tract infections and other diseases. In the experiments the DNA (i.e., all the genetic information, including

the tumor producing genes) of the above described polyoma virus will be spliced onto a bacterial virus (called lambda phage) or a plasmid, which is a self-replicating piece of DNA, akin to a virus. The plasmid or phage containing the polyoma tumor virus genes will then be inserted into E. coli, where it will be replicated. Whether an E. coli bacterium that contains the genetic information for polyoma tumor virus production will cause cancer in humans or other warm blooded animals, or what kinds of cancers it will cause, what their symptoms will be, how they can be treated, or anything else about the nature of this new organism is unknown. Such an organism is not known to exist in nature.

4. Although precautions may be devised against the escape of the newly created organisms, we know from past experience that human error is unavoidable, and the consequences of escape into the atmosphere of the newly created organisms may occur. Because of their novelty, the effect upon the environment of the new organisms and the symptoms of their action upon the environment can not be known in advance. The nature of the organisms to be created by this research is such that, if released from containment, they may remain dormant in the environment for a substantial period of time, and continue to possess the potential for infecting the environment. In addition, the natures of the organisms are likely to be such that it would be only after a substantial amount of the population is infected that the trouble could be traced to these organisms, and by this time the infection can have spread far and wide. This is due in part to the fact that the organisms may evoke symptoms that

are new, may take 20 to 30 years to cause cancer symptoms, or may imitate other diseases. Also unknown are the methods of treatment of any illnesses caused by the new organisms.

5. The greatest danger of these experiments is that the hazard is alive, self-perpetuating, and reproduces rapidly. Once out, it can not be recalled. If released into polluted waters, such as the Potomac River, even relatively small quantities of organisms can rapidly multiply to the point where large populations are threatened. Conduct of such experiments in laboratories contiguous to a large populated area, upstream from a water supply source already reputed to be polluted, unnecessarily exposes the population to many unpredictable health hazards.

6. The E. coli to be utilized in the experiments is a "weakened" strain, as opposed to the natural, "wild type" strain. It is not known whether the weakened strain, when combined with the mouse cancer genes can exchange genetic information with other, wild type strains, but such exchanges occur commonly among different E. coli strains and among E. coli and other microorganisms. The wild type strains of E. coli inhabit the whole environment, living in soil, water and all warm blooded animals, and are carried by insects and fish. If such genetic interchange did occur, there is absolutely no way of predicting what segment of the environment polyoma virus that has been mixed into a wild type E. coli will infect. However, this possibility clearly poses a threat t

warm blooded animals and indeed to the entire environment.

7. It has been asserted that the "weakened" bacteria used as gene implantation recipients in the experiments have an outside survival probability of one in one hundred million. However, one quart (reasonable daily working quantity) of laboratory culture of recombinant DNA, the product of the gene splicing experiments, easily contains 10-100 million bacteria. Even a miniscule quantity of harmful organisms in the environment, due to their ability to reproduce rapidly, represents a real danger. The possibilities of grave and unknown risks of the spread of cancer, of slow viruses, or of novel pathogens can not be discounted. Such agents could well become widely disseminated before their noxious effects became evident.

8. The experiments proceed on the assumption, stated as a fact, that polyoma virus only infects rodents and is not a human cancer virus. However, research sufficient to establish the truth of that statement has not been conducted. Polyoma virus was first discovered in 1960, and to date no scientific study has been published as to the incidence of cancer among the laboratory workers who have worked with polyoma over those 17 years. And 17 years since exposure to a carcinogen is not an overly long induction period for cancer. To say that polyoma is not a human cancer therefore violates fundamental, accepted, scientific practice, due to the present state of knowledge (or ignorance) of the virus and of cancer epidemiology. However,

even if the premises were correct, since the E. coli with which cancer virus is to be combined is known to live in people, there is no way of knowing in advance if the combination of the two will result in an organism capable of causing cancer in humans.

9. The protocol states that the National Institutes of Health intends to make "inactivated bacterial lysates available to interested investigators." This means that the E. coli cells containing the polyoma cancer genes will be burst open (lysed) and will no longer be able to reproduce by themselves. Yet the genetic information is still active within such lysates and can be transferred to other living cells in which it can then reproduce. The protocol implies that the lysates will not be provided P-4 containment--the highest form of safety--and will not be subject to the safeguards that exist at earlier stages in the genetic combination research. Such lysates present at least as much of a hazard as the recombinant E. coli, which are afforded P-4 treatment, in that they can be dispersed in dust and air, and because the inactivated lysate is able to infect other E. coli, or might be taken up by the cells of the investigator. A real threat of contamination of the environment exists under this portion of the protocol.

Ruth Hubbard

STATE OF MASSACHUSETTS)
SS.
COUNTY OF Barnstable)

Personally appeared before me, the undersigned, a Notary Public in and for the State and County aforesaid Ruth Hubbard, who made oath in due form of law that the foregoing affidavit is true.

WITNESS my hand and notarial seal this 28 day of May, 1977.

Mary E. Angevine
Notary Public

Notary Public in and for the State of Massachusetts, County of Barnstable

My Commission Expires: 1981

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR., an infant,

Plaintiff :

v. : Civil Action No. 77- 0916

JOSEPH A. CALIFANO, JR., ET AL.,

Defendants :

FILED

MAY 31 1977

JAMES F. DAVEY, Clerk

AFFIDAVIT IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER

1. I, Christine Oliver, am a physician, an assistant in Medicine at Massachusetts General Hospital, an instructor in Medicine at Harvard Medical School, and Board Certified in Internal Medicine.

2. I have read and am familiar with a document entitled Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells, by Martin and Rowe (the "Protocol"), for the conduct of experiments in Building 550 at Ft. Detrick, Maryland.

3. These experiments involve the use of polyoma virus, which is known to cause cancer in mice and other rodents. The experiments also employ the bacterium, E. coli, which lives on land and in water all over the earth, and in particular is a common

inhabitant of the large intestine of all warm blooded animals, including humans. Some strains of E. coli are known to cause diarrhea, urinary tract infections and other diseases. In the experiments the DNA (i.e., all the genetic information, including the tumor producing genes) of the above described polyoma virus will be spliced onto a bacterial virus (called lambda phage) or a plasmid, which is a self-replicating piece of DNA, akin to a virus. The plasmid or phage containing the polyoma-tumor virus genes will then be inserted into E. coli, where it will be replicated. Whether an E. coli bacterium that contains the genetic information for polyoma tumor virus production will cause cancer in humans or other warm blooded animals, or what kinds of cancers it will cause, what their symptoms will be, how they can be treated, or anything else about the nature of this new organism is unknown. Such an organism is not known to exist in nature.

4. Although precautions may be devised against the escape of the newly created organisms, we know from past experience that human error is unavoidable, and the consequences of escape into the atmosphere of the newly created organism may occur. Because of their novelty, the effect upon the environment of the new organisms and the symptoms of their action upon the environment can not be known in advance. The nature of the organisms to be created by this research is such that, if released from containment, they may remain dormant in the environment for a substantial period of time, and continue to possess the potential for infecting the environment. In addition, the natures of the organisms are likely to be such that

it would be only after a substantial amount of the population is infected that the trouble could be traced to these organisms, and by this time the infection can have spread far and wide. This is due in part to the fact that the organisms may evoke symptoms that are new, may take 20 to 30 years to cause cancer symptoms, or may imitate other diseases. Also unknown are the methods of treatment of any illnesses caused by the new organisms.

5. The greatest danger of these experiments is that the hazard is alive, self-perpetuating, and reproduces rapidly. Once out, it can not be recalled. If released into polluted waters, such as the Potomac River, even relatively small quantities of organisms can rapidly multiply to the point where large populations are threatened. Conduct of such experiments in laboratories contiguous to a large populated area, upstream from a water supply source already reputed to be polluted, unnecessarily exposes the population to many unpredictable health hazards.

6. The E. coli to be utilized in the experiments is a "weakened" strain, as opposed to the natural, "wild type" strain. It is not known whether the weakened strain, when combined with the mouse cancer genes can exchange genetic information with other, wild type strains, but such exchanges occur commonly among different E. coli strains and among E. coli and other microorganisms. The wild type strains of E. coli inhabit the whole environment, living in soil, water and all warm blooded animals, and are carried by insects and fish. If such genetic interchange did occur, there is

absolutely no way of predicting what segment of the environment polyoma virus that has been mixed into a wild type E. coli will infect. However, this possibility clearly poses a threat to all warm blooded animals and indeed to the entire environment.

7. It has been asserted that the "weakened" bacteria used as gene implantation recipients in the experiments have an outside survival probability of one in one hundred million. However, a one quart (reasonable daily working quantity) of laboratory culture of recombinant DNA, the product of the gene splicing experiments, easily contains 10-100 million bacteria. Even a miniscule quantity of harmful organisms in the environment, due to their ability to reproduce rapidly, represents a real danger. The possibilities of grave and unknown risks of the spread of cancer, of slow viruses, or of novel pathogens can not be discounted. Such agents could well become widely disseminated before their noxious effects became evident.

8. The experiments proceed on the assumption, stated as a fact, that polyoma virus only infects rodents and is not a human cancer virus. However, research sufficient to establish the truth of that statement has not been conducted. Polyoma virus was first discovered in 1960, and to date no scientific study has been published as to the incidence of cancer among the laboratory workers who have worked with polyoma over those 17 years. And 17 years since exposure to a carcinogen is not an overly long induction period for cancer. To say that polyoma is not a human cancer violates fundamental,

accepted, scientific practice, due to the present state of knowledge (or ignorance) of the virus and of cancer epidemiology. However, even if the premise were correct, since the E. coli with which cancer virus is to be combined is known to live in people, there is no way of knowing in advance if the combination of the two will result in an organism capable of causing cancer in humans.

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Christine Oliver

STATE OF MASSACHUSETTS)
ss.
COUNTY OF NORFOLK)

Personally appeared before me, the undersigned, a Notary Public in and for the State and County aforesaid Christine Oliver, who made oath in due form of law that the foregoing affidavit is true.

WITNESS my hand and notarial seal this 28TH day of MAY, 1977.

Notary Public

Notary Public in and for the State of Massachusetts, County of Norfolk

My Commission expires
March 21st 1981

PROPOSED EXPERIMENTS ON THE BIOLOGICAL PROPERTIES OF POLYOMA RECOMBINANT DNA CLONED IN BACTERIAL CELLS

77- 0916

FILED
MAY 3 - 1977
JAMES F. DAVEY, Clerk

Malcolm A. Martin
Laboratory of Biology of Viruses
National Institute of Allergy and Infectious Diseases

Wallace P. Rowe
Laboratory of Viral Diseases
National Institute of Allergy and Infectious Diseases

EXHIBIT No. 1

During the past year, considerable interest has developed regarding the potential benefits and biohazards associated with the production of recombinant DNA molecules and their subsequent amplification in both prokaryotic and eukaryotic cells.

Many individuals have felt that an experiment involving the cloning of polyoma DNA in E. coli, using either a lambdaphage or plasmid vector, and the subsequent inoculation of mice with the resultant bacterial cultures, would be highly informative. We have been charged by the N.I.H. Advisory Committee on Recombinant DNA to plan and carry out such experiments utilizing facilities of suitable containment that are available to N.I.H. intramural scientists in Bethesda. It should be noted that these experiments are being done on the basis of an exemption from the San Diego guidelines voted by the N.I.H. Advisory Committee.

The reasons for selecting polyoma virus for such an experiment are manifold. Polyoma virus DNA is small (3×10^6 daltons), is well characterized chemically and physically, and is infectious; the virus appears to represent no biohazard to man. However, the chief reason for its selection is the well-documented observation that parenteral inoculation of mice with minimal doses of virus regularly leads to an immune response (Rowe et al., Journal of Experimental Medicine, 109, 379, 1959; Rowe et al., Perspectives in Virology, 2, 177, 1961). This phenomenon is the basis for the mouse antibody production (MAP) test for polyoma virus. In this assay, mice from a polyoma-free colony are injected with test material and, three to four weeks later, are tested for serum hemagglutination inhibiting (HI) antibody against the virus. This test can detect approximately one tissue culture infectious dose (TCID) of polyoma virus; adults are as sensitive as suckling mice. Feeding and intranasal instillation of virus are much less efficient modes of infection. We thus view the

HI antibody to be a highly sensitive, unambiguous and convenient test for the occurrence of a productive polyoma infection in mice. It is especially appealing in the context of the proposed studies which involve the use of an E. coli cloning system because it is a continuing test (i.e. a single group of mice, colonized by an E. coli plasmid or phage system containing a polyoma component, can be tested repeatedly for whether productive virus infection has occurred at any time during the prolonged period of observation).

In the following paragraphs we outline a series of experiments which will utilize polyoma virus to answer some of the questions which have been raised about potential biohazards of recombinant DNA research. Specifically, we intend to generate recombinant molecules consisting of polyoma virus and bacteriophage lambda DNAs or polyoma virus and plasmid (Col E1 or a derivative thereof) DNAs, and clone such molecules in a suitable E. coli host. Progeny phage, as well as plasmid-containing E. coli will be fed to, and inoculated into mice, in the final step of the proposed experiments and the animals tested for evidence of virus infection. Although, at first sight, this seems to be a simple, straightforward experiment which could be done cheaply and expeditiously, this is not the case. In particular, since we are very concerned that a negative result will be misinterpreted as indicating that there is little biohazard in DNA recombinant work, we feel that a number of variables must be evaluated, and that the experiments should be designed to maximize the chances of a positive result. Also, if negative results are obtained with a given system, we feel that the experiments should be continued with modified systems until we are reasonably convinced that a positive result is just not going to occur. Variables to be considered, in roughly decreasing order of importance, are: the strain(s) of phage and type(s) of plasmid;

the strain(s) of E. coli; the topology and orientation of the inserted DNA (chiefly, whether present as a tandem insertion or a single copy); the route of administration; whether colonization occurs, the presence or absence of intestinal bacteria, the nature of the intestinal flora, and the age of the mice when first exposed.

Carrying out these experiments will also provide an opportunity to study the related question of the possible biohazard of handling biologically active DNA, and we plan to include studies of the infectivity of polyoma DNA administered by various routes.

At the present time we foresee these studies being carried out in three stages. Depending on the results obtained and barring any unanticipated technical problems, stages 1 and 2 should be completed within 6 to 8 months. The third stage, which will involve the use of a plasmid vector system, will require the cloning and selection of bacteria containing the desired recombinant molecules under P4 conditions. We anticipate that stage three can be completed within nine months to a year.

The experiments enumerated below represent our current ideas regarding how such an endeavor should proceed. In no way should they be construed as the final protocol for the studies proposed. We are presently contacting investigators both within and outside the NIH who we feel can make a significant contribution toward the planning and execution of the project.

STAGE 1. Infection of Mice with Biologically Active and Potentially Biologically Active Materials

This stage will have two objectives: to determine the infectivity of polyoma DNA when given by ingestion, inhalation and injection; and to provide certain baseline data needed for design of the mouse experiments.

These studies will include:

1. Titration of polyoma DNA *in vivo* by the MAP procedure using:
   a) oral, intranasal and subcutaneous routes
   b) DNA in: physiological saline, DEAE-dextran, and calcium phosphate
   c) conventional and, if possible, germ-free mice of weanling age

2. Any necessary studies on the ability of the *E. coli* system to colonize germ-free mice and on its pathogenicity following parenteral inoculation. Roy Curtiss (University of Alabama) will play a large role in selecting the strain, and will be able to supply much of this information.

STAGE 2. The Preparation of Recombinant DNA Molecules Consisting of Polyoma and Bacteriophage Lambda Components and their Subsequent Inoculation into Test Animals.

A. DNA

1. *Polyoma*

Plaque purified polyoma virus (large plaque strain) will be propagated as described by Winocour (Virology 19, 158-168, 1963). Virus will be purified by equilibrium density centrifugation in CsCl and the supercoiled DNA isolated by dye-buoyant density centrifugation in CsCl-ethidium bromide. The homogeneity of closed circular polyoma DNA will be assessed by electrophoresis in 1.4% agarose slab gels and cleavage with R *Hind*. Unique full-length linear molecules of polyoma DNA will be prepared with *Eco* R1 enzyme and isolated by sucrose gradient centrifugation or agarose slab gel electrophoresis.

2. Lambdaphage

λgt-λB will be obtained from Dr. Ron Davis, Stanford University and propagated as described by Thomas et al. (PNAS 71, 4579-4583, 1975) in E. coli strain C600. Phage DNA will be purified as described by Thomas and Davis (J. Mol. Biol. 91, 315-329, 1975) and cleaved, initially analytically, and then preparatively, with R·Eco RI.

B. Ligation and Transfection

1. Preparation of oligomeric polyoma DNA

a) Eco RI linear molecules of polyoma DNA (50 ugm/ml) will be incubated with T4 ligase in the presence of 0.1 M Tris-HCl, pH 7.9, 50 mM NaCl, 1.0 mM EDTA, 12 mM $MgCl_2$, 10 mM DTT, 0.1 mM ATP and 0.1 ug/ml bovine serum albumin at 10°C.

b) A sample of the reaction mixture will be analyzed by electrophoresis through 0.7% agarose. If suitable amounts of oligomeric polyoma DNA have been generated, the entire reaction mixture will be subjected to preparative agarose gel electrophoresis and dimeric through tetrameric polyoma DNA bands eluted from the gels.

2. Preparation of polyoma-bacteriophage lambda recombinant DNA molecules

a) Eco RI cleaved lambda DNA (50 µg/ml) will be briefly heated to dissociate terminal sequences and incubated with oligomeric forms of polyoma DNA (50 µg/ml) in 0.1M Tris-HCl, pH 7.9, 50 mM NaCl, 1.0 mM EDTA, 12 mM $MgCl_2$, 10 mM DTT, 0.1 mM ATP, 0.1 µg/ml bovine serum albumin and T4 ligase at 10°C.

b) A sample of the reaction mixture will be checked for evidence of ligation by electrophoresis in 0.7% agarose, restriction enzyme cleavage patterns and electron microscopic analysis of heteroduplexes.

3. If the studies carried out in 2b indicate that recombinant DNA molecules consisting of polyoma oligomers and bacteriophage lambda sequences have been generated (which we will designate P-lambda), an aliquot of the reaction mixture will be used to transfect the C600 strain of E. coli K-12 in the presence of 50 mM $CaCl_2$ under P-4 conditions.

4. P-lambda phage will be purified from infected cultures under P-4 conditions and the DNA isolated will be incubated with various restriction enzymes and analyzed by gel electrophoresis to ascertain if polyoma DNA has replicated in E. coli.

C. Biological Activity of Cloned Recombinant DNA (Carried out under P-4 conditions)

1. Infection of mouse cells in culture.

Primary mouse embryo cells in culture will be infected with the crude cell lysate, purified P-lambda recombinant DNA, and with P-lambda bacteriophage. Polyoma virus will be detected by CPE, indirect immunofluorescence of infected cells and a blind passage thereof.

2. Infection of mice.

a) Adult and newborn mice will be inoculated subcutaneously and intraperitoneally with varying amounts of bacteriophage P-lambda in both free and "contained" (i.e. in E. coli freshly infected with the phage) forms.

b) Germ-free and conventional mice will be infected intranasally and orally with varying amounts of free and contained recombinant P-lambda phage.

c) In all cases animals will be tested for the development of polyoma HI antibody, and, possibly, tumor formation. It is anticipated that the immunologic assays can be performed under P2-conditions provided it can be demonstrated that heat-treated serum (56°-30 min.) is free of E. coli or bacteriophage lambda.

a) samples of feces from mice infected by the oral route will be examined for the presence of polyoma virus.

STAGE 3. The Preparation of Recombinant DNA Molecules Consisting of Polyoma and Col E 1 Components and their Subsequent Inoculation into Test Animals

A. DNA

1. Polyoma DNA will be purified and cleaved with R·Eco R1 as described in Stage 2, A1.

2. Col E1 plasmid, or a derivative thereof (obtained following consultation with Dr. Herbert Boyer, U.C., San Francisco) will be prepared from an appropriate strain of E. coli K-12. Purity of plasmid DNA will be assessed by agarose gel electrophoresis and cleavage with appropriate restriction endonucleases.

B. Ligation and Transfection

1. Oligomeric polyoma DNA will be prepared as described in Stage 2, B1.

2. Eco R1 cleaved Col E1 DNA, or a derivative thereof, will be ligated to oligomeric forms of polyoma DNA in the reaction mixture outlined in Stage 2, B2(a).

3. A sample of the reaction mixture will be examined for evidence of ligation as described in Stage 2, B2(b).

4. Transformation of E. coli will be effected as described by Cohen et al. (PNAS 69, 2110-2114, 1972) in the presence of 0.003 M $CaCl_2$ under P-4 conditions. Approximately twenty clones will be characterized. Initally, the clones will be screened by nucleic acid hybridization and subsequently by heteroduplex analysis and digestion of supercoiled DNA with restriction endonucleases. The bacterial clone containing the

desired plasmid DNA will be grown in mass culture in the presence of chloramphenicol to amplify the plasmid element.

5. Plasmid DNA will be purified from infected cultures and assessed for the presence of polyoma DNA sequences with appropriate restriction enzymes and heteroduplex techniques.

C. Biological Activity of Cloned Recombinant DNA (Carried out under P-4 conditions).

1. Infection of mouse cells in culture

Primary mouse embryo cells in culture will be infected with purified recombinant plasmid DNA in the presence of DEAE-dextran. Polyoma virus will be detected by CPE, indirect immunofluorescence of the infected cells and a blind passage thereof.

2. Infection of mice

a) Adult and newborn mice will be inoculated subcutaneousl and intraperitoneally with varying amounts of E. coli containing Col El-polyoma recombinant plasmids, a bacterial cell lysate, and with purified recombinant plasmid DNA.

b) If polyoma HI antibody develops in the animals inoculat parenterally, germ-free and conventional mice will be infected with varying amounts of E. coli containing recombinant plasmids by the oral and nasal routes.

c) If polyoma HI antibody is not detected following the parenteral administration of recombinant plasmid and plasmid DNA, mice will be inoculated with a bacterial clone containing a different plasmid DNA recombinant by the parenteral route. The recombinant plasmid from the initial clone would not be used to infect mice by the oral and nasal routes since it seems very unlikely that seroconversion would occur in the face of a negative result following parenteral administration of such plasmid material.

d) In all cases, animals will be tested for the development of polyoma HI antibody and tumor formation.

e) Samples of and feces from mice infected by the oral route will be examined for the presence of polyoma virus.

3. We also contemplate further studies to evaluate the *E. coli* containing recombinant DNA and will focus on such parameters as growth properties, the colonization of germ-free mice, and the transmission and mobilization of recombinant plasmid elements.

Since we do not plan to examine the transcription and translation of polyoma DNA in either of the prokaryotic systems under study, we intend to make inactivated bacterial lysates available to interested investigators. Such studies could conceivably yield important new information about other possible mechanisms of biohazard.

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR., an infant Plaintiff	:	Smith, J.
v	:	Civil Action No. 77-0916
JOSEPH A. CALIFANO, JR. et al. Defendants	:	FILED JUN - 9 1977 JAMES F. DAVEY, Clerk

SUPPLEMENTAL MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION

Plaintiff has heretofore filed herein a motion for a temporary restraining order and preliminary injunction, and a memorandum of points and authorities in support thereof.

In addition to the foregoing, there is annexed hereto and designated Exhibit #7, an editorial from the New England Journal of Medicine, May 26, 1977, pages 1226-1228, which further reflects the continuing controversy between eminent scientists as to the course the research should take.

Although the documents indicating it were attached as exhibits to the original memorandum filed herein, the point that the funds utilized for construction of the Ft. Detrick laboratory have never been legally authorized was not made. In defendant Nutter's letter of May 2, 1977 (Exhibit #3), he states that:

> "The expenditure of funds under this contract was authorized by Ronald H. Defilice, contracting officer, NCI, FCRC (A). The use of laboratories in Building 550 for recombinant DNA research was approved by the Director of NIH and complies with the intent of Congress (Enclosures B and C). "

Exhibit #3C to the memorandum, which is Exhibit C to Nutter's letter, is a portion of a transcript of testimony which defendants contend authorized the expenditure of the funds. However, a reading of the transcript reveals no such authorization. What is said, is the following:

> "At next year's hearings [1977] the Committee would welcome a report on the potential usefulness to NIH of the unused buildings and equipment at Ft. Detrick together with cost estimates for whatever modifications are required to adapt them to productive biomedical research."

No such report or estimate was provided to Congress; no Congressional authorization for conversion of the Ft. Detrick facility to biomedical research is, by the defendants' own admissions, existent.

The posture of compliance with NEPA by the defendants is this:

(a) Defendant Frederickson has concluded that an environmental impact assessment should be done on the proposed guidelines for the conduction of recombinant DNA research. (Federal Register Volume 41, No. 131--Wednesday, July 7, 1976, page 27906)

(b) A "draft environmental impact statement" on the guidelines for recombinant DNA research has been prepared and circulated (Federal Register Volume 41, No. 176--Thursday, September 9, 1976, page 38426).

(c) No final environmental impact statement has been prepared on the guidelines for conduction of recombinant DNA research.

(d) No final environmental impact statement has been prepared for the conduction of the experiments proposed at Ft. Detrick.

The disregard by the defendants in this case of the requirements of NEPA is such that the language of the court in Scherr v Volpe 466 F.2d 1027 (1972) (7th Circuit) is appropriate:

> "Next the defendants submit that the injunction should not have issued inasmuch as the plaintiffs failed to show that the construction of Highway 16 would result in irreparable harm to the environment. The defendants' argument in this respect proceeds from the premise that even though there be a clear violation of the Act, even though, as the district court stated, the responsible federal agency failed to "assemble all pertinent information, to subject it to expert scrutiny and to articulate clearly and in writing an evaluation of the various benefits and costs which are being balanced", that no judicial relief may be afforded the plaintiffs absent a showing on their part that the project would be damaging to the environment. We think the district court's rejection of this theory is particularly relevant: "to suggest that when the federal agencies flatly fail to perform this function, a plaintiff in a lawsuit such as this suit must perform it as a condition to obtaining injunctive relief is to suggest that one of the central purposes of the Act be frustrated." To accept the defendants' argument on this point would thwart the Congressional mandate by rendering impotent the procedural requirements of the National Environmental Policy Act of 1969. What this argument attempts to do is to shift the burdens of considering and evaluating the environmental consequences of particular federal actions from the agencies Congress intended to bear them to the public, the beneficiary of this legislation. If these agencies were permitted to avoid their responsibilities under the Act until an individual citizen, who possesses vastly inferior resources, could demonstrate environmental harm, reconsideration at that time by the responsible federal agency would indeed be a hollow gesture."

As our Court of Appeals observed in Calvert Cliffs' Coord. Com. v United States, 449 F.2d 1109 at 1115:

> "[T]he Section 102[NEPA] duties are not inherently flexible. They must be complied with to the fullest extent, unless there is a clear conflict of statutory authority."

For the foregoing and such other and further reasons as may be urged that the orally hearing of this motion, plaintiff moves that a temporary restraining order in the form of that annexed hereto be entered by the Court.

Respectfully submitted

Ferdinand J. Mack
17 West Jefferson Street
Suite 106
Rockville, Maryland 20850
279-2230

CERTIFICATE OF MAILING

I HEREBY CERTIFY that a copy of the foregoing Supplemental Memorandum of Points and Authorities in Support of Motion for Preliminary Injunction was mailed, postage prepaid to the U.S. Attorney, Earl J. Silbert on the 7th day of June, 1977.

The New England Journal of Medicine

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JUN - 9 1977 [Appendix C--91]

PUBLIC-HEALTH POLICY AND RECOMBINANT DNA

The issue of recombinant DNA research (i.e., gene manipulation) has been discussed widely in the public press and scientific journals. The controversy has been the focus of numerous meetings sponsored by the National Institutes of Health and most recently by the National Academy of Sciences. It is regrettable, therefore, that the report in this issue of the *Journal* by C. Cohen completely ignores the central questions in the debate. It dismisses potential hazards associated with the technology while attempting to lay down a priori principles on which to make judgments of little relevance. The report is an entertaining intellectual exercise with no bearing on the facts involved. Worse yet, Cohen demonatrates a lack of understanding of science and its history, and particularly of the specifics of recombinant DNA research. The real issue — a determination of sound public-health policy taking into account both potential benefits and hazards — is not addressed. Rather, the bulk of his thesis revolves around questions of complete prohibition, a position not shared even by critics of the research whose views, in my opinion, he so distorts. Cohen seems unaware of the difference between reasonable constraint, a view espoused to varying degrees by most of those on both sides of the debate, and absolute prohibition. This view sets back the controversy instead of constructively helping to define the issues. It is a disservice to the proponents of the research who have struggled so diligently at self-regulation.

Recombinant DNA technology makes it possible to remove DNA from any organism, to chop the DNA enzymatically into smaller sequences of genes, to splice these genes into an appropriate vector (usually a virus or plasmid), and then to use the vector to infect an animal, plant or bacterial cell of choice. The end result then is the insertion of the foreign genes of interest into a new host. This revolutionary technic permits genetic information to cross species barriers readily. It has allowed genes derived from animal cells and their viruses to be implanted into bacteria, and bacterial genes to be inserted into animal cells. The usual "time gap" (a potential safety valve) between a fundamental discovery in basic science and its application as a technology disappeared in record time with recombinant DNA studies. With its capacity to rearrange the genetic heritage of millions of years of evolution, this technology appears to offer a power to transform living organisms comparable to the power of nuclear fission to transform matter.

Recombinant DNA technology will have profound effects on biomedical sciences, industry and society at large. There is indeed the potential for benefits of large magnitude. With regularity, bacteria are now being implanted with nonbacterial genes. These genes are then reproduced as the genetically modified bacteria reproduce, thereby making it possible to obtain the gene products for which the implanted genes code.

So programmed, bacteria are envisioned as factories for the production of hormones, antibiotics, antibodies and enzymes of potential use in medicine and industry, as well as other gene products needed for basic research. So engineered, the normal control systems regulating bacterial growth and function may be circumvented.

Recombinant DNA technology is now in widespread use in basic-research laboratories, with the number of such experiments constantly increasing. A not unreasonable estimate is that 10^{15} to 10^{16} recombinant organisms per year will be produced in the laboratories and that this number will be substantially increased by industrial involvement.[1] Like the benefits of nuclear-power plants, the benefits of recombinant DNA research are likely to come with mixed peril. The National Institutes of Health and other proponents of the technology are to be lauded for their efforts in struggling with this dilemma and the resultant development of guidelines for future studies. In some instances these guidelines seem particularly effective when dealing with the more obvious concerns of public-health nature by prohibiting overtly dangerous classes of experiments — for example, the cloning of recombinant DNA's from known oncogenic viruses or pathogens.[2]

The real shortcoming of the guidelines is that they do not give equal importance to potential problems developing from less obvious situations than the known pathogens mentioned above. The enormous complexity of micro-organisms and ignorance of their intricately complicated ecology make it impossible to predict with certainty the end effect of any transplant of large numbers of genes into the micro-organism of choice, *Escherichia coli* K-12, or a further enfeebled genetically modified strain derived from K-12. *Esch. coli* is indigenous to human beings and all warm-blooded animals, is carried by many other organisms such as insects and fish, and can be found throughout the biosphere in soil and water. This microbe can normally exchange genetic information with 40 other species of micro-organisms, and though the likelihood of exchange from the genetically enfeebled strain has been markedly reduced, it still may occur. The vast sea of micro-organisms in the environment makes events whose probability is the reciprocal of Avogadro's number (i.e., $1/10^{23}$) not impossible.*

Many experiments being carried out employ "shotgun" technics where complete chromosomes of undefined gene sequence are split into many segments followed by insertion of these unknown genes into *Esch. coli* with potentially unpredictable results. Every implanted gene becomes a new hypothesis, and there will be tens of thousands of such new hypotheses inserted. This is the "Catch-22" dilemma associated with the technology. Could we inadvertently, via unexpected transfer of genetic information from the enfeebled host strain to one of the estimated 10^{13} to 10^{14} healthy *Esch. coli* organisms in the human bowel, create a novel self-replicating pathogen? Do we know for certain the effect in human beings or any other creature of the biosphere, of a novel micro-organism producing a powerful insulin-like hormonal activity? Cloning of the insulin gene is but one of many experiments now in progress, any of which could have potential toxic or autoimmune effects. What effect might such a micro-organism have on other varieties of enfeebled hosts — the human patients who are on antibiotics therapy, who are immunosuppressed or who are otherwise debilitated by disease. In some cases these patients reside in hospitals that also include recombinant DNA research laboratories. We do not as yet know the answers to the above questions. These questions should be addressed, and their answers and solutions framed in a new and badly needed public-health policy.

That the NIH is providing millions of dollars for construction of containment facilities for some of this research is to its credit. Yet the "Fort Detrick Experience"[3] and the records of the Center for Disease Control make it painfully clear that absolute containment of micro-organisms is impossible — even in laboratories where workers are exceedingly well trained and experienced in working with pathogenic organisms. Human frailty will guarantee mistakes. What, then, can be expected from numerous new laboratories recently involved in recombinant DNA research whose personnel have at best had a three-day course on containment procedures? Here, we have the potential for a unique form of pollution, biologic pollution, and it will be distinguished by its irreversibility. In contrast to nuclear-power plants, which can be closed down, micro-organisms will reproduce and perpetuate themselves. They cannot be recalled. Unlike the defined pathogens studied at Fort Detrick, their escape cannot be monitored for.

The great deal of time and effort put into self-regulation, and the development of biologic and physical containment systems by the proponents of the technology, is unprecedented. They have set an example of genuine concern for human well-being and the biosphere. But they have not faced containment of their own exponentially expanding activities, which may be an equally irreversible route to ecologic disaster at the rate at which the research activities are expanding. In reality, we have all become experimental subjects for recombinant DNA experiments. Yet none of us have signed an informed-consent statement.

A risk-assessment panel has recently been convened by the NIH to determine the risks involved and where information is lacking to propose experiments to obtain the information. This is a proper and important step in terms of public-health considerations. The burden of proof or lack of hazards should rest neither on the opponents nor on the proponents of the research. Their role should simply be to distill and define the issues for the remainder of the biomedical

*Curtis R: Potential biohazards of recombinant DNA molecules (unpublished memorandum to Paul Berg et al.) August 6, 1974.

community and the public at large. The go-ahead signal should be the result of a public-health decision-making process, developed by decision-making bodies democratically appointed and representative of a rich diversity of ethical and scientific points of view.

And in the interim? I believe that the research should proceed, but on a more limited basis, perhaps only at regional facilities of high containment staffed by experienced and well trained personnel. A host bacterium less ubiquitous than *Esch. coli* also seems a wiser choice. Such a temporary slowdown would have no effect on freedom of inquiry. Rather, it would effect freedom of manufacture — the manufacture of novel self-replicating micro-organisms. A miscalculation on our part as scientists would have far more damaging effects than a temporary slowdown on science as we know it in terms of public outrage and mistrust.

The societal benefits that may well arise from gene transplantation studies will be valuable whether they come in 20 years versus 25, or 50 years versus 55. These benefits and the sheer excitement and beauty of scientific endeavor will endure for centuries thereafter. For five or 10 years now, a slow, thoughtful approach to limiting hazards makes sense in terms of progressive public-health policy.

Harvard Medical School
Boston, MA 02115 RICHARD GOLDSTEIN, PH.D.

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FILED

JUL 18 1977

JAMES F. DAVEY, Clerk

FERDINAND J. MACK, JR., Plaintiff, v. JOSEPH A. CALIFANO, JR., et al., Defendants.	Civil Action No. 77-916

STIPULATION

It is hereby stipulated by and between counsel for the parties hereto as follows:

1. All proceedings in this matter shall be stayed pending the finalization by defendants of an Environmental Impact Statement.

2. Defendants shall give to counsel for plaintiff thirty (30) days notice of any experiment to be conducted at Fort Detrick, Maryland, on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells, and no such experiment shall be conducted at Fort Detrick prior to the finalization of an Environmental Impact Statement.

3. Counsel for defendants shall immediately inform the Court and counsel for plaintiff upon the finalization of an Environmental Impact Statement, and the stay of proceedings shall be vacated at that time.

4. Defendants shall have fifteen (15) days from the date on which the stay is vacated, within which to respond to plaintiff's motion for a preliminary injunction. A hearing on the motion for preliminary injunction shall be scheduled at some convenient date subsequent thereto.

Ferdinand J. Mack /dkf
FERDINAND J. MACK, ESQUIRE
Attorney for Plaintiff

David R. Schlee
DAVID R. SCHLEE
Assistant United States Attorney
Attorney for Defendants

APPROVED:

UNITED STATES DISTRICT JUDGE

July 18, 1977
DATED

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. An Infant	:	
Plaintiff	:	Civil Action 77-0916
v	:	
JOSEPH A. CALIFANO, JR. et al.	:	
Defendants	:	

FILED

DEC - 8 1977

JAMES F. DAVEY, Clerk

RESPONSE OF PLAINTIFF TO DEFENDANTS' MOTION FOR VACATION OF STAY

Ferdinand J. Mack, Jr., an infant, plaintiff, for answer to the request contained in the defendants' "Notice of Filing" that the stay of this Court entered herein July 18, 1977, be vacated by the Court, respectfully represents to the Court as follows:

1. This is an action having as its primary purpose the prohibition of experiments termed "risk assessment studies" which defendants seek to conduct at Ft. Detrick, Maryland. The experiments are technically entitled "Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells" (Complaint, page 4).

2. On July 18, 1977, at the request of the defendants, a stay was entered into in the form of a stipulation which was signed by counsel for plaintiff and defendants, and approved by the Court. That stipulation provided in pertinent part:

> "Defendants shall give to counsel for plaintiff thirty (30) days notice of any experiment to be conducted at Ft. Detrick, Maryland, on the biological properties of polyoma recombinant DNA cloned in bacterial cells, and no such experiments shall be conducted at Ft. Detrick prior to the finalization of an environmental impact statement."

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

3. On November 30, 1977, defendants served upon plaintiff a "Notice of Filing" indicating that the defendants had filed with the Court a "Final Environmental Impact Statement in this matter." In that "Notice of Filing" the defendants requested that the stay--the subject matter of the stipulation of July 18, 1977, "now be vacated by the Court at its convenience."

4. Having entered into the stipulation, and sought and obtained Court approval of the same, the defendants cannot unilaterally withdraw from that stipulation, and even if plaintiff were to consent, which he does not, would still require Court approval of release from the stipulation. The stay should not be vacated for the following reasons:

(a) The "Environmental Impact Statement in this matter" which defendants advert to relates only to "the release of the NIH Guidelines for Research Involving Recombinant DNA Molecules." (EIS pg. iii) That (EIS) does not address the subject matter of this action, namely the risk assessment studies, referred to above. The only reference in the EIS to the subject matter of this action, is at page 101 of Volume I, of the EIS, as follows:

> "Virologists of the National Institute of Allergy and Infectious Diseases are preparing to conduct experiments at the Frederick Cancer Research Center, Frederick, Maryland, which should provide data to help determine if recombinant DNA research could result in real hazards."

(b) It is precisely these experiments--designed to "determine if recombinant DNA research could result in real hazards" which this action seeks to enjoin. However, this experiment is not the subject matter of this or any other environmental impact statement.

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

(c) Further evidence that the Environmental Impact Statement upon which defendants rely is not addressed to the subject matter of this action is found in the fact that no consideration is given in the EIS to the effect of the Ft. Detrick experiments on the air, water, population, sewerage capacity or other peculiar environmental circumstances of Frederick County, Maryland, where Ft. Detrick is located.[1] The Environmental Impact Statement indicates no attempt on the part of the Government to solicit the views, opinions, and ascertain the desires of the residents of the community where these

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[1] The Guidelines for preparation of environmental impact statements, promulgated by the Council on Environmental Quality (36 Fed. Reg. 7724-29, April 23, 1971 and 38 Fed. Reg. 10856, May 2, 1973) provide that the particular action proposed must be addressed in terms of impact on the environment. The regulations, require an EIS to contain, in part:

> "(i) A description of the proposed action including information and technical data adequate to permit a careful assessment of environmental impact by commenting agencies. Where relevant, maps should be provided.
>
> (ii) The probable impact of the proposed action on the environment, including impact on ecological systems such as wildlife, fish, and marine life. Both primary and secondary significant consequences for the environment should be included in the analysis. For example, the implications, if any, of the action for population distribution or concentration should be estimated and an assessment made of the effect of any possible change in population patterns upon the resource base, including land use, water, and public services, of the area in question.
>
> (iii) Any probable adverse environmental effects which cannot be avoided (such as water or air pollution, undesirable land use patterns, damage to life systems, urban congestion, threats to health or other consequences adverse to the environmental goals set out in Section 101(b) of the Act)."
>
> ....

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
50 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2250

risk assessment studies are to be conducted.[2]

(d) If what the Government proposes to do in this case is proper, there would have been no need to consider the Alaskan environment in an EIS on the Alaskan Pipeline; and any EIS on super highways (without regard to where located) would satisfy the requirements of an EIS relating to Route 66 in the crowded Virginia suburbs of Washington, D.C. If this disregard of the law is what defendants intended when they signed the stipulation, it was not entered into in good faith on their part, and they should not be released from their commitment to this Court.

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[2] The Guidelines also place upon the agencies involved "a responsibility to develop procedures to insure the fullest practicable provision of timely public information and understanding of Federal plans and programs with environmental impact in order to obtain the views of interested parties. These procedures shall include, whenever appropriate, provisions for public hearings, and shall provide the public with relevant information...." (Guidelines, Section 309 10(e)) The sequence of events involving the risk assessment studies is that the Guidelines, and the draft EIS on the Guidelines, were both promulgated before the public was made aware of the risk assessment studies to be conducted at Ft. Detrick, and no opportunity to comment upon the proposed Environmental Impact Statement as it might be related to the risk assessment studies was afforded to the public. Comments on the Environmental Impact Statement were required to be submitted before November 1, 1976, and notice to the public of the proposed risk assessment studies at Ft. Detrick was not given until early 1977.

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE MARYLAND
20850

301 279-2230

5. There presently exists in this case a stipulation which stays the conduction of "Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells" at Ft. Detrick. On the state of the present record, this Court should not relieve the Government from the burden of that stay.

Ferdinand J. Mack
17 West Jefferson Street
Suite 106
Rockville, Maryland 20850
Attorney for Plaintiff

CERTIFICATE OF MAILING

I hereby certify that a copy of the foregoing was mailed, postage prepaid this 7th day of December, 1977, to David R. Schlee, Assistant U.S. Attorney, U.S. District Courthouse, Room 3438-B, Washington, D.C. 20001.

Ferdinand J. Mack

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850
301 279-2230

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR.,

Plaintiff,

v.) Civil Action No. 77-916

JOSEPH A. CALIFANO, JR. et al.,

Defendants.

FILED

DEC 13 1977

JAMES F. DAVEY, Clerk

DEFENDANTS' REPLY TO PLAINTIFF'S RESPONSE FILED DECEMBER 7, 1977

On December 7, 1977 plaintiff responded to defendants' Notice of Filing, to which an environmental impact statement is appended. Our notice of filing suggests that, since an environmental impact statement has now been finalized and submitted to the Court, it is now appropriate for the Court to lift the stay of proceedings approved July 18, 1977.

Plaintiff opposes a lifting of the stay on the ground that the environmental impact statement submitted with our notice of filing is not in compliance with the National Environmental Policy Act, 42 U.S.C. §§4320 et seq. This simply makes no sense. The sufficiency of our environmental impact statement is the central issue in this case, and is to be resolved on the merits. However, in order to rule on the merits it is quite necessary for the Court to lift the stay of proceedings.

Plaintiff's primary objection to the environmental impact statement seems to be that the statement addresses the environmental impacts of recombinant DNA research performed in accordance with the NIH Guidelines, but does not specifically address the particular individual experiment which is the subject of plaintiff's action. However, the law is clear that, in appropriate circumstances, agencies may issue broad program statements in lieu of statements with respect to each individual action encompassed by a program. National Resources Defense Council v. TVA (Coal Purchases), 367 F.Supp. 122, 127 (E.D. Tenn. 1973), aff'd, 502 F.2d 852 (6th Cir., 1974); Minnesota Public Interest Research Group v. Butz, 498 F.2d 1314, 1323, n.29 (8th Cir. 1974); Fund for the Animals v. Frizzell, 402 F.Supp. 35 (D.D.C. 1975), aff'd., 530 F.2d 982, 988, n. 15 (D.C.

Cir. 1976); District I-Marine Engineers v. Coleman, Civil Action No. 75-1208 (D.D.C. 1975); East Tennessee Energy Group, Inc., v. Seamans, 7 ERC 2144 (D.D.C. 1975). As we will demonstrate in our opposition to plaintiff's motion for a preliminary injunction, the environmental impact statement submitted to the Court in this case falls within the ambit of the above cases. A broad program statement with respect to recombinant DNA research satisfies the requirements of NEPA, and individual impact statements with respect to each and every recombinant DNA experiment are unnecessary.

Thus, it is apparent that there is no point whatsoever in continuing the stay of proceedings here. An environmental impact statement has been finalized and submitted to the Court. That environmental impact statement complies fully with NEPA, and we shall so demonstrate to the Court in our opposition to plaintiff's motion for a preliminary injunction. Moreover, plaintiff will have a full opportunity to attempt to show the Court why the environmental impact statement is not sufficient with respect to the particular experiment which is the subject of his action. In these circumstances, the stay of proceedings should be lifted so that the Court can consider the merits of the complaint.

Respectfully submitted,

Earl J. Silbert

EARL J. SILBERT
United States Attorney

Robert N. Ford per ejk

ROBERT N. FORD
Assistant United States Attorney

David R. Schlee

DAVID R. SCHLEE
Assistant United States Attorney

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that I have served a copy of the foregoing Reply upon plaintiff, pro se, Ferdinand J. Mack, Suite 106, Old Town Center, 17 West Jefferson Street, Rockville, Maryland 20850, on this 12th day of December, 1977.

DAVID R. SCHLEE
Assistant United States Attorney
U.S. District Courthouse
Room 3438-B
Washington, D.C. 20001
(202) 426-7154

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, Plaintiff, v. JOSEPH A. CALIFANO, Jr., et al., Defendants.	916 Civil Action No. 77-~~919~~

FILED

DEC 30 1977

JAMES F. DAVEY, Clerk

AFFIDAVIT

I, John E. Nutter, Ph.D., being duly sworn, depose and say:

1. I am the Chief of the Office of Specialized Research and Facilities, National Institute of Allergy and Infectious Diseases, National Institutes of Health. I am a microbiologist and have worked in the field for over 20 years.

2. The NIH Guidelines for Recombinant DNA Research stipulate that P4 physical containment and EK2 biological containment must be employed during the preparation of recombinant DNA molecules that include all or part of animal virus DNA. The experiment at issue in this lawsuit, to be conducted by Dr. Wallace Rowe and Dr. Malcolm Martin, will be carried out in full compliance with these containment requirements.

3. In imposing such stringent requirements on the preparation of such recombinant DNA molecules, the Guidelines reflect a conservative and prudent approach to containment, designed to avoid any risk of harm to laboratory personnel, the community, and the environment. In fact, however, the

Rowe/Martin experiment poses no added risk to humans or the environment because: (1) polyoma virus (the animal virus being used) does not itself grow in human cells and has not been shown to be associated with any human diseases; (2) it is already widely disseminated in the environment, as evidenced by its recovery from the urine and saliva of both urban and rural populations of wild mice; and (3) in the laboratory, it produces tumors only when injected into newborn hamsters and mice (tumors have never been found in wild mice).

3. The Environmental Impact Statement (at page 4) emphasizes the fact that the current Guidelines are very conservative. The purpose of the Rowe/Martin experiment is to develop information which will be used in assessing whether the containment levels specified in the Guidelines are appropriate. It must be emphasized, however, that the planned experiment will still conform to the Guidelines as fully as any other research project involving the same materials and techniques.

4. Further delay in the conduct of this experiment will significantly hinder our ability to critically evaluate hypothetical risks associated with recombinant DNA research which may warrant changes in the Guidelines. A continuing inability to conduct this experiment is likely to result in delaying significant changes in the Guidelines that may be scientifically desirable.

John E. Nutter

John E. Nutter, Ph.D.
Chief, Office of Specialized
Research and Facilities
National Institute of Allergy
and Infectious Diseases
National Institutes of Health

SUBSCRIBED AND SWORN TO
BEFORE ME THIS 30th DAY
OF DECEMBER, 1977.

Sharon Fulton
Notary Public

My commission expires October 31, 1980

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK,

Plaintiff,

v.

JOSEPH A. CALIFANO, Jr., et al.,

Defendants.

77-0916

Civil Action No. ~~77-919~~

FILED

DEC 30 1977

JAMES F. DAVEY, Clerk

DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFF'S MOTION FOR A PRELIMINARY INJUNCTION

Preliminary Statement

Plaintiff seeks to prevent an experiment to be undertaken in Building 550, Frederick Cancer Research Center, Fort Detrick, Maryland. The experiment will test the biological properties of polyoma recombinant DNA cloned in bacterial cells,[1/] and plaintiff contends that defendants have not prepared an environmental impact statement covering the experiment in accordance with §102(2)(C) of the National Environmental Policy Act, 42 U.S.C. §4322(2)(C).

In order to obtain preliminary injunctive relief, plaintiff must satisfy the well-known standards of Virginia Petroleum Jobbers Assn. v. F.P.C., 259 F.2d 921, 925 (D.C. Cir. 1959). He must establish (1) that he will be irreparably injured in the absence of preliminary injunctive relief; (2) that defendants will not be irreparably injured if such relief is granted; (3) that there is a substantial likelihood that he will prevail on the merits; and (4) that the public interest favors issuance of an injunction. Here, plaintiff will not be irreparably injured in the absence of an injunction because,

1/ For purposes of convenience, we will refer to the experiment at issue in this case simply as "the experiment".

as we demonstrate below, the experiment to be conducted at Fort Detrick poses no significant threat to him or to the environment. Moreover, plaintiff is totally unable to demonstrate any likelihood that he will prevail on the merits because defendants have complied fully with the requirements of NEPA. To the contrary, a preliminary injunction halting this important experiment will deprive the public and the scientific community of important and much-needed information.

Plaintiff will not prevail on the merits. On November 28, 1977, the Council on Environmental Quality published a notice in the Federal Register of the availablity of the Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules (hereinafter "EIS"), submitted to it by the National Institutes of Health (NIH), United States Department of Health, Education and Welfare (HEW). 42 Fed. Reg. 60588. This EIS complies fully with all requirements of NEPA. Moreover, the EIS constitutes a broad program statement which is acceptable under 40 C.F.R. §1500.6(d)(1), and there is absolutely no need for the preparation of a separate environmental impact statement for each and every recombinant DNA experiment which is conducted.[2/] Finally, it is apparent that plaintiff misunderstands the materials to be used in the experiment to be conducted at Fort Detrick. These materials are far safer than the ones plaintiff describes in his complaint.

Statement

The preparation of the NIH Guidelines and accompanying environmental impact statement reflects the especially cautious

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2/ While the EIS primarily assesses the impact of the NIH Guidelines regarding recombinant DNA research, it also assesses the impact of experiments conducted under the Guidelines. (See especially, EIS at 99-112). The experiment at issue in this case will be conducted in full accordance with the NIH Guidelines.

manner in which the scientific community and NIH have approached the new technology involving recombinant DNA molecules.

Prior to the promulgation of the NIH Guidelines in 1976, the scientific community operated for several years under a voluntary moratorium on certain kinds of recombinant DNA experiments. EIS at 15-17. The ability to perform recombinant DNA experiments was first generally recognized in 1973. Id. In response to concerns expressed about the unknown possibilities of the technique, NIH organized an Advisory Committee in 1974 to advise it on appropriate controls on the research and participated in a conference at Asilomar, California, in 1975. Id. The Asilomar Conference developed voluntary guidelines which were substantially followed throughout the scientific community. Id. at 17-19. NIH recognized the need for more formal guidelines and began to prepare them. Id. at 19-20. As part of this process, a public meeting was held by NIH on February 9 and 10, 1976, at which issues concerning the research and the Guidelines were discussed. Prior to the meeting, a Federal Register announcement was published indicating the subject, time and place of the meeting, the person to be contacted for materials and further information, that the public could attend, and that both oral and written comments were welcome. 41 Fed. Reg. 2105 (January 14, 1976).

Thereafter, NIH published the "Decision of the Director, NIH," and the Guidelines in full in the Federal Register on July 7, 1976. 41 Fed. Reg. 27902 (1976). The Guidelines apply to all NIH-funded research and require that before such research employing recombinant DNA techniques may proceed, a Memorandum of Understanding and Agreement (MUA)

must be submitted and approved by NIH. EIS at 22. Compliance with the MUA is monitored by local biohazards committees. Id.

In addition, NIH prepared a draft environmental impact statement discussing the environmental impacts of the Guidelines and of recombinant DNA techniques conducted under the Guidelines. Indeed, NIH took the unusual step of publishing the draft EIS in the Federal Register to insure the widest possible public dissemination and comment. 41 Fed. Reg. 38426 (September 9, 1976). Public comment on the draft was voluminous. See Final EIS at App. K. Moreover, detailed responses to the comments were also made. EIS at 113. In addition to the extensive discussion of the Guidelines and of their environmental impacts, a lengthy discussion of alternatives is included. EIS at 65-88. Further detail is contained in the Appendices to the Final EIS.

Argument

I. Separate Environmental Impact Statements Are Not Required For Each Individual Experiment.

Plaintiff's argument appears to be that defendants have failed to comply with NEPA because they have not prepared a separate impact statement for the individual experiment to be conducted at Fort Detrick. Defendants have not prepared a separate statement for the experiment at Fort Detrick, and such a statement would serve no purpose since the research complies with the NIH Guidelines. The EIS which we have filed with the Court fully assesses the environmental impact of all recombinant DNA research conducted in accordance with the NIH Guidelines, and individual statements for each experiment are unnecessary and would be duplicative.

Significantly, the Guidelines of the Council on Environmental Quality (CEQ) and other CEQ pronouncements favor the preparation of multi-action EISs covering numerous individual activities. The CEQ Guidelines specifically place the responsibility for determining the scope of statements on the agency and contemplate preparation of programmatic statements:

> Agencies should give careful attention to identifying and defining the purpose and scope of the action which would most appropriately serve as the subject of the statement. In many cases, broad program statements will be required in order to assess the environmental effects of a number of individual actions on a given geographical area (e.g., coal leases), or environmental impacts that are generic or common to a series of agency actions (e.g., maintenance or waste handling practices), or the overall impact of a large-scale program or chain of contemplated projects (e.g., major lengths of highway as opposed to small segments). Subsequent statements on major

> individual actions will be necessary where such actions have significant environmental impacts not adequately evaluated in the program statement.

40 C.F.R. §1500.6(d)(1) (emphasis supplied). Moreover, CEQ has strongly endorsed program statements in its Fifth Annual Report entitled "Environmental Quality" (December 1974) (at p. 413, emphasis added):

> The Council has strongly encouraged agencies to prepare program statements. Frequently, basic policy issues in the operation of a program can be addressed only in an analysis which covers the whole program; at the project level, it is often not feasible to review these basic questions. In addition, preparation of a program statement may allow an agency to dispense with the preparation of impact statements on individual projects, provided that impacts at the site are not substantial. Even if such impact statements cannot be dispensed with, however, they can often be reduced in size if the program statement already covers many of the impacts. Thus, preparing program statements may help to increase the efficiency of the NEPA process.

Also, CEQ has stated "[i]n particular we are interested in finding ways of consolidating numbers of impact statements into fewer but broader and more meaningful reviews." CEQ, "Recommendations for Improving Agency NEPA Procedures", quoted with approval in Natural Resources Defense Council v. TVA (Coal Purchases), 367 F.Supp. 122, 127 (E.D. Tenn. 1973), aff'd, 502 F.2d 852 (6th Cir. 1974). These CEQ interpretations of NEPA should be given "great respect" by this Court. See Sierra Club v. Morton, 169 U.S. App. D.C. 20, 514 F.2d 856, 873 (D.C. Cir. 1975), rev'd on other grounds, sub. nom., Kleppe v. Sierra Club, 427 U.S. 390 (1976).

In Coal Purchases, supra, the Sixth Circuit affirmed the trial court's opinion which held that TVA, which had prepared a programmatic impact statement on its purchases of coal, did not have to prepare individual impact statements on each specific coal purchase contract.

In Minnesota Public Interest Research Group v. Butz, 498 F.2d 1314, 1323 n.29 (8th Cir. 1974), the court noted that upon preparation of an overall management plan for a particular national forest area, individual impact statements on each timber sale or other management activity would not be required.

Three decisions by this district court have also strongly endorsed the concept of programmatic impact statements instead of individual impact statements.

First, in Fund for the Animals v. Frizzell, 402 F.Supp. 35 (D. D.C., 1975), aff'd, 530 F.2d 982, 988 n.15 (D.C. Cir. 1976), plaintiff sought an injunction against waterfowl hunting regulations of the Fish and Wildlife Service where the Service had prepared a comprehensive statement on its overall sport hunting program. The injunction was denied, in part because Interior had prepared a programmatic impact statement concerning overall sport hunting of migratory birds. 402 F.Supp. at 37.

Second, in District 1 - Marine Engineers v. Coleman, Civil Action No. 75-1208 (D. D.C. 1975), plaintiffs sought impact statements on certification of individual tankers where the Coast Guard had prepared an impact statement on environmental regulations which controlled the environmental standards of individual tankers. In rejecting this claim, the court held that separate impact statements were not needed (sl. op. at 7, emphasis added):

> NEPA may be satisfied when an agency develops an impact statement for an entire program. CEQ Guidelines, 40 C.F.R. §1500.6(a)(1974). Thus, the Coast Guard's EIS covers regulations which will govern all oil tankers such as the ones at issue here. It would in this Court's opinion,

> be futile to require that an impact statement be prepared for each tanker when these vessels admittedly conform to construction design regulations which are meant to protect the environment, and for which an EIS has already been prepared.

Similarly, the experiment here will conform to the Guidelines and to the policies discussed in the EIS.

Third, in East Tennessee Energy Group, Inc. v. Seamans, 7 ERC 2144 (D. D.C. 1975), an injunction was sought halting proposals for funding a specific breeder reactor plant which was included in the programmatic statement being prepared on the liquid metal fast breeder reactor program (LMFBR). In denying plaintiffs' motion for a preliminary injunction, the Court correctly noted that individual EISs were not needed (7 ERC at 2145):

> [A]s the 'prototype' plant, the Clinch River project is subsumed into the overall LMFBR impact statement. ERDA need not pause at this juncture to re-evaluate the individual project as long as the LMFBR statement performs a cost benefit analysis on the total program and its component parts and weighs carefully all available alternatives.

Under these cases and CEQ pronouncements, programmatic impact statements do provide a way for federal agencies to comply with NEPA without preparation of numerous duplicative and unnecessary individual impact statements.[3/]

3/ We use the term "programmatic impact statement" to refer to the EIS on the NIH Guidelines which we have previously filed with the Court. As the EIS recognizes, there is no "Recombinant DNA Program" as such since recombinant DNA techniques are part of other research: "Recombinant DNA technology is essentially a tool used in many programs, funded from many sources. In this sense, it is analogous to a new instrument or radioisotopes." EIS at 17.

Recently, the Supreme Court has summarized the limited role of the courts in determining whether agencies have complied with NEPA:

> Neither the statute nor its legislative history contemplates that a court should substitute its judgment for that of the agency as to the environmental consequences of its actions. [Citation omitted.] The only role for a court is to insure that the agency has taken a 'hard look' at environmental consequences; it cannot 'interject itself within the area of discretion of the executive as to the choice of the action to be taken'.] Natural Resources Defense Council v. Morton, 458 F.2d 827, 838, 148 U.S. App. D.C. 5, 16 (1972).

Kleppe v. Sierra Club, 427 U.S. 390, 410 n.21 (1976). In Carolina Environmental Study Group v. United States, 166 U.S. App. D.C. 416, 418, 510 F.2d 796, 798 (1975), the court elaborated on the test of adequacy:

> [NEPA's] language requires description of reasonably foreseeable effects. A 'rule of reason' is used to ascertain those effects anticipated. [Citation omitted.] The 'detailed statement' is required as a basis for intelligent balancing of the effect on the environment with the economic and technical factors. [Citation omitted.]

The EIS does represent a "hard look" by NIH at recombinant DNA research performed in accordance with its Guidelines. After describing in detail the background of the recombinant DNA experimental process, as well as discussing the issues raised by recombinant DNA research, the EIS describes in detail its action and the alternatives to it. The EIS then discusses in detail the possible environmental impact not only of the NIH Guidelines, but also of recombinant DNA research conducted in accordance with the Guidelines.

Because the experiment complies with the NIH Guidelines and because compliance with the Guidelines insures

that no recombinant DNA molecules will escape from the carefully controlled laboratory to the environment, a separate EIS discussing the environment at Fort Detrick or at Frederick, Maryland, would serve no purpose. NIH has adopted comprehensive Guidelines concerning all facets of recombinant DNA research, and these Guidelines essentially eliminate adverse environmental impacts. Under the Guidelines recombinant DNA research will be conducted in such a way as to eliminate significant environmental impacts at individual locations. Hence, the Guidelines set forth detailed physical containment requirements to prevent the escape of all organisms together with biological containment requirements to ensure that any escaping organisms do not survive outside the laboratory. The EIS fully assesses the environmental impact of research performed in accordance with these requirements of the Guidelines, and there is no need whatsoever for NIH to engage in the useless analysis of individual factors in each geographic location where an experiment is conducted.

As discussed in Part II below, much of plaintiffs' concern is based on an apparent misunderstanding of the nature of the materials to be used in the experiment. Significantly, the NIH "Guidelines prohibit certain kinds of recombinant DNA experiments, which include all the known hazards -- for example, those involving known infectious agents." Final EIS at 2. Plaintiff has presented no evidence to suggest that the experiment poses any threat to the environment at all. The use of maximum containment facilities

specifically certified to make escape virtually impossible,[4/] combined with biological containment so that if any research material did escape it could not survive, insure that there is virtually no possibility of any adverse environmental impact from this experiment.

II. Plaintiff Misunderstands The Host To Be Used In the Experiment Here.

Plaintiff appears to believe that the experiment here in question will be conducted utilizing common strains of Escherichia coli (E. coli) as the host bacterium for the planned studies. (See complaint, ¶9). Such strains of E. coli do have an ability to survive in nature, and do "live in people." During the past 35 years, scientists around the world have used a strain of E. coli (E. coli K-12) which has been adapted for use in laboratory studies. E. coli K-12 is unable to colonize the human intestinal tract, causes no known human or animal disease and poses no threat to the environment. See EIS at 73. In the planned experiment, a derivative of E. coli K-12, which has been specifically designed to "self-destruct", will be employed. This EK2 host-vector system will not survive passage through the intestinal tract of animals and would "die" because of its dependency on chemicals not found in nature. For each certified EK2 system (listed on page H-10 of the EIS) NIH reviews extensive scientific data to determine that the system meets the Guideline standards for safety. EIS at 81. See NIH Guidelines, EIS App. D, p. 15. Thus, there is actually a two-step distinction between the common strains

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4/ The P4 facility is completely isolated from all other areas of the building and has various engineering facilities designed to prevent the escape of micro-organisms. In addition, all recombinant DNA materials are handled in gas-tight biological safety cabinets and are removed only after sterilization. More detail concerning P4 containment is found in the EIS at 51-52.

of E. coli which do "live in people" and the EK2 host-vector systems which will be used in these experiments.

The inherent safety of E. coli K-12 and the EK2 host-vector systems are discussed on pages 53-55 and 73-81 of the EIS, and Appendix H to the EIS. Some relevant passages of the EIS include:

> E. coli K-12 appears to be a harmless microorganism. It does not usually establish itself in the normal bowel or multiply significantly in the alimentary tract. . . . (EIS at 53).
>
> There is considerable difference between the ecology and epidemiology of K-12 and those E. coli strains that are pathogenic or commonly inhabit mammalian intestinal tracts. (EIS at 73).
>
> The laboratory variants of K-12 to be used in recombinant DNA experiments have never been reported to cause disease, even in laboratory workers. K-12 has been grown in very large quantities (up to hundreds of liters containing up to 10^{12} -- that is, 1,000,000,000,000 -- bacteria per liter at a time) in hundreds of laboratories all over the world over a period of 30 years and under containment conditions lower than those specified as P1 in the Guidelines. . . . (EIS at 74).
>
> [E]ven after normal humans have ingested up to 10^{10} (10,000,000,000) K-12 cells, only transient multiplications of the bacteria in the intestines can be observed, and ... after a time no K-12 can be detected in the feces. Thus, K-12 does not establish itself as a permanent resident of normal human beings. (EIS at 74).

It must also be pointed out that the complete experiment will be conducted in P4 physical containment laboratories. Such laboratories have been shown to safely contain microbes with a known and demonstrable infectious hazard to man and other animals. The basic physical containment device in this instance is a stainless steel and glass system of closed glove-boxes. All exhaust air is decontaminated before discharge and all research materials must be treated to sterilize them before

they are removed. Additionally, all waste materials from the entire facility (including sewage) are sterilized before discard as a redundant safety measure. Therefore, before any harm could ensue, the recombinant DNA molecules would have to escape the physical containment measures (an extremely unlikely possibility) and the vector-host system would have to multiply or secondarily transmit the DNA in nature (an almost inconceivable possibility; see EK2 specifications) and then cause some untoward event which the whole, intact virus has never been shown capable of inducing.

Accordingly, plaintiff's attack upon the safety of the experiment to be performed at Fort Detrick is premised upon the totally false assumption that the host organism to be utilized can readily survive outside the laboratory, and is able to "live in people." Plaintiff further assumes that some dangerous organism may escape from the rigid physical containment required. Since both assumptions are false, plaintiff has failed to show that he or the environment will be irreparably injured by this experiment.

III. Further Delay In The Experiment Will Deprive Scientists Of Important Information Concerning Recombinant DNA Molecules.

As explained in the Nutter Affidavit, the experiment is designed to provide important and much needed information on the possibilities of recombinant DNA technology. Further delay in obtaining this knowledge will leave an unnecessary gap in scientific understanding of recombinant DNA technological possibilities.

As Dr. Nutter and the EIS both note, the NIH Guidelines were intentionally written in a conservative manner and thus may be overly cautious. This experiment is designed to test whether some of the fears expressed about possibilities of risks from recombinant DNA research are in fact scientifically possible. Yet, this risk assessment experiment itself poses no threat because the particular virus has never been implicated in human disease, because it is widely found in nature and because, in any event, it is being handled in maximum physical and biological containment.

Significantly, important information about the possibilities of recombinant DNA technology will be delayed should plaintiff's motion for a preliminary injunction be granted. As Dr. Nutter notes, this knowledge is important in determing whether the NIH Guidelines need revision. Delay in gaining this knowledge could delay significant changes in the Guidelines that may scientifically prove to be desirable.

Accordingly, since the experiment poses virtually no risk to man or the environment and since delay in conducting this important experiment deprives NIH and the scientific community of important knowledge concerning the possible risks of recombinant DNA technology, the public interest and equities clearly favor a denial of plaintiff's motion.

Conclusion

For the foregoing reasons, plaintiff has failed to satisfy the standards necessary for the issuance of preliminary injunctive relief. Accordingly, defendants

respectfully request that plaintiff's motion for a preliminary injunction be denied.

Respectfully submitted.

Earl J. Silbert

EARL J. SILBERT
United States Attorney

Robert N. Ford per sch

ROBERT N. FORD
Assistant United States Attorney

David R. Schlee per sch

DAVID R. SCHLEE
Assistant United States Attorney

L. Mark Wine

L. MARK WINE
Land and Natural Resources Division
Department of Justice

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that I have served copies of the foregoing Opposition and Affidavit of John Nutter upon plaintiff by mailing a copy thereof to Ferdinand Mack, Esquire, 17 West Jefferson Street, Rockville, Maryland 20850, on this 30th day of December, 1977.

David R. Schlee

DAVID R. SCHLEE
Assistant United States Attorney
U. S. District Courthouse
Room 3438-B
Washington, D. C. 20001
426-7154

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FILED
JAN 12 1978
JAMES E. DAVEY, Clerk

FERDINAND J. MACK, JR. an infant	:	
Plaintiff	:	Civil Action No. 77-0916
v	:	
JOSEPH A. CALIFANO, JR. et al	:	
Defendants	:	Judge John Lewis Smith, Jr.

SUPPLEMENTAL MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION AND IN OPPOSITION TO VACATION OF STAY

1. This action started out as an endeavor to compel the defendants to file an environmental impact statement before they commenced the proposed Risk Assessment Studies at Ft. Detrick, Frederick, Maryland As the Court is aware, defendants have stipulated that the experiments will not proceed until an environmental impact statement is prepared. Thus, the issue is no longer whether an environmental impact statement should be prepared in connection with these experiments; the issue is whether a legally sufficient environmental impact statement has been prepared.

2. The questions confronting the Court in reviewing the environmental impact statement filed by defendants are: (1) Is the environmental impact statement on guidelines for all DNA research one that addresses the proposed Risk Assessment Studies? and (2) Does the statement comply with the requirements of NEPA?

3. The defendants concede that the environmental impact statement does not address itself specifically to the Ft. Detrick Risk Assessment Studies:

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

> "Defendants have not prepared a separate statement for the experiment at Ft. Detrick,.... the EIS which we have filed with the Court fully assesses the environmental impact of all recombinant DNA research conducted in accordance with the NIH Guidelines, and individual statements for each experiment are unnecessary and would be duplicative." (Defendants' Memorandum in Opposition to Plaintiff's Motion for Preliminary Injunction, p. 5)

4. Throughout the Government's opposition, perhaps unintentionally, runs the thread that to grant plaintiff the relief sought in this case would create havoc, because the ruling would be applicable to all DNA experiments. For example:

> "[T]here is absolutely no need for the preparation of a separate environmental impact statement for each and every recombinant DNA experiment which is conducted." (Defendants' Memo p. 2)
>
> "[I]ndividual statements for each experiment are unnecessary and would be duplicative." (Defendants' Memo p. 5)
>
> "[T]here is no need whatsoever for NIH to engage in the useless analysis of individual factors in each geographic location where an experiment is conducted." (Defendants' Memo p. 10)

This action is not directed at "each and every recombinant DNA experiment" which is conducted. Plaintiff's attack is only upon the Risk Assessment Studies, the purpose of which is to determine if a "real hazard" exists in DNA research; it is concerned only with the Risk Assessment Studies at Ft. Detrick.

5. In arguing that the Risk Assessment Studies are covered by the environmental impact statement for the guidelines, it would appear that the defendants are attempting to hoist themselves up by their own

FERDINAND J. MACK
ATTO..NEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

bootstraps. They are at the same time arguing that the defendants' guidelines eliminate adverse environmental impacts, (Defendants' Memo p. 10) and at the same time arguing that the environmental impact statement covers an experiment necessary to determine whether "real hazards" exist from DNA research. (Environmental Impact Statement p. 101)

6. Significantly omitted from the environmental impact statement are alternatives to the proposed Risk Assessment Studies, although required by § 102 (2) (C) (iii)[1]

At page 65 of the statement, it is stated:

> Description of Alternatives
>
> The following general classes of action have been considered as alternatives to, or additions to, the issuance of NIH Guidelines for Recombinant DNA Research ...

It must be pointed out that the alternatives are to DNA research, and not to the conduction of the Risk Assessment Studies the subject of this action. No alternatives to the conduction of these experiments are considered, in any way in the impact statement, although the guidelines of the Council on Environmental Quality state that a "Rigorous exploration and objective evaluation of alternative actions that might avoid some or all of the adverse environmental effects is essential ." (SS 6 (IV) (Emphasis added) Not only is there no statement on the alternatives to the proposed Risk Assessment Studies, but the statement is further deficient because it fails to comply with § 102 (2) (D) of NEPA which requires the agency to "study, develop, and describe appropriate alternatives."

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE MARYLAND
20850
301 279-2230

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1 There is authority to the effect that these alternatives be contained in a detailed statement on "alternatives to the proposed action" Environmental Defense Fund v Corps of Engineers (Gillham Dam), Appendix B, 470, F 2d 289

7. Not only have defendants attempted to violate NEPA, they are attempting to avoid their own HEW regulations. HEW procedures for NEPA compliance apply to individual research projects, as well as entire research programs. DHEW General Administrative Manual, Sections 30-11-00, 30-12-00. Section 30-12-00 states:

> "Actions which are a part of a program or group of activities that do not have a Statement of Inapplicability (Chapter 30-11-20) to the NEPA requirements, must be reviewed on an individual basis to determine the extent of the effects the action would have on the environment." (Emphasis added)

8. As defendants have stated, the Risk Assessment Studies are designed "to help determine if recombinant DNA research could result in real hazards." (Environmental Impact Statement p. 101)

The argument by defendants that a broad environmental impact statement is adequate under these circumstances, is not convincing. Moreover, the cases relied upon by the defendants do not furnish the support for the circumstances confronting the Court here.

In National Resources Defense Council v TVA 367 F. Supp 122, relied on by the defendants, the Court held that there was "a rational basis for TVA's determination that compliance with NEPA could be accomplished by filing a single program statement." 367 F. Supp 122, 128. No rational basis for following that precedent can be asserted in the present case where the experiment under attack is necessary to assure safety of all DNA research.

In Minnesota Public Interest Research Group v Butz, 498 F 2d 1314, also relied upon by the defendants, the issue before the Court was whether an environmental impact statement was required, and in affirming an injunction on timber cutting until the statement was

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

prepared on overall policy, the court stated, in a footnote:

> "We are of the view that upon consideration of the overall timber management policy of the Forest Service in an EIS complying with NEPA, each administrative action taken pursuant to that policy will not require a separate impact statement. In other words, if the environmental effects of timber cutting are considered in the overall EIS, an individual EIS for each timber sale would not be required, absent a material change in circumstances or a departure from the policy covered in the overall EIS." 498 F 2d 1323, Footnote 29

It must be borne out that in the present case, as opposed to MPIRG v Butz, supra, the environmental effects are largely unknown, and potentially lethal. It is precisely because they are unknown, that the Risk Assessment Studies are being conducted.

East Tennessee Energy Group Inc. v Seamans, 7 ERC 2144, likewise relied upon by the defendants, is not supportive of their position. There the plaintiffs sought to compel the Energy Research and Development Administration to withdraw a legislative proposal for appropriations, pending compliance with NEPA. The legislation was already moving through Congress and involved previous legislation, and many other complexities of the Liquid Metal Fast Breeder Reactor Program.

A case not cited by defendants is National Resources Defense Council v Morton, 388 F Supp 829. There the Bureau of Land Management prepared a draft programmatic statement on its entire livestock grazing program. Plaintiffs asked for and received, detailed individual statements prepared on an appropriate district or geographic level, to assess the actual impact of the issuance of the Federal grazing permits on local environments, the court distinguishing the case from NRDC v TVA, Supra.

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

9. Ominously missing from the environmental impact statement, although required by NEPA, is an assessment of the potential damage to life and health of the residents of Frederick County, Maryland, should the organisms involved in the experiments react in an untoward way, and should they escape laboratory containment. By their very arguments that the experiments pose "virtually" no risk to man or the environment, (Memo p. 14) and that the maximum containment facilities make escape "virtually" impossible and that there is "virtually" no possibility of any adverse environmental impact from this statement, (Memo p. 10-11) defendants concede the possibility of the unthinkable contamination of the environment with a novel disease which may cause illness, death, and untold harm to this and future generations. Despite this frightening scenario, simple questions, like--Are there other facilities where the experiments can be conducted which are more removed from the population centers than at Ft. Detrick? How much would it cost to prepare suitable facilities for the conduction of these experiments at other locations? How much time would it take to prepare other suitable facilities?--are not answered--not even addressed--by defendants.

The defendants accept the possibility of escape of the organisms from the experimental confinement. They acknowledge that these organisms could result in real hazards to health, for it is for this very reason that the Risk Assessment Studies are to be conducted. But more than six months have elapsed since defendants became aware that the processes of this Court would be utilized to force an environmental impact statement on the Risk Assessment Studies and rather than utilizing that time in a good faith effort to prepare a statement on these experiments, they have instead attempted to side step the issue rather

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
[illegible] WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

than meet it in a forthright fashion. One wonders if the stipulation was entered into by the Government in good faith, or was simply a device to avoid an inevitable order to prepare an environmental impact statement.

10. Defendants predicate their opposition to a preliminary injunction in large part upon a claim that plaintiff has not shown that he has met the traditional criteria for determination of granting preliminary injunctive relief. Those are (1) the probability of plaintiff's success on the merits; (2) irreparable harm to the plaintiffs pendente lite; (3) the balance of hardships between the parties; and (4) where appropriate, as here, the public interest. Virginia Petroleum Jobbers Association v F.P.C., 259 F 2d 921, 925 (D.C. Cir. 1958).

However, when a federal statute has been violated, the rule has been that a court need not inquire into the traditional requirements for equitable relief. United States v City and County of San Francisco, 310 U.S. 16, [illegible] S.Ct. 749 (1940) (Court affirmed injunction of action in violation [illegible]deral "Raker" Act); Atchison, Topeka and Santa Fe Railway Co. v Callaway, 382 F. Supp. 610, 623 (D.D.C. 1974) (NEPA violation); Lathan v Volpe, 455 F 2d 1111, 1116, (9th Cir. 1971) (NEPA violation); Community Nutrition Institute v Butz, 420 F. Supp. 751 (D.D.C. 1976) (Court enjoined regulation promulgated in violation of the Administrative Procedure Act and the Federal Meat Inspection Act).

11. Even though the traditional criteria for equitable relief need not be established in this case because of its very nature, nevertheless, plaintiff has established the irreparable injury that is required. In Jones v District of Columbia Redevelopment Land Agency, 499 F 2d 502, 512 (D.C. Circuit 1974), the Court stated:

[illegible]NAND J. MACK
[illegible]TORNEY AT LAW
[illegible] 100
[illegible] TOWN CENTER
[illegible] JEFFERSON ST.
[illegible]VILLE, MARYLAND
[illegible]
[illegible]

> "The harm against which NEPA's impact statement requirement was directed was not solely or even primarily adverse consequences to the environment; such consequences may ensue despite the fullest compliance. Rather NEPA was intended to ensure that decisions about federal actions would be made only after responsible decision makers had fully adverted to the environmental consequences of the actions and had decided that the public benefits flowing from the actions outweighed their environmental costs. Thus the harm with which courts must be concerned in NEPA cases is not strictly speaking, harm to the environment, but rather the failure of decision-makers to take environmental factors into account in the way that NEPA mandates. And for the purposes of deciding whether equitable relief is appropriate, we think that this harm matures simultaneously with NEPA's requirements, i.e., at the time the agency is, under NEPA obliged to file the impact statement and fails to do so."

The usual requirements that for preliminary injunctive relief to lie, the Court must balance the probability of plaintiff's success on the merits is, as indicated above, not strictly required because of the nature of this action. However, even if plaintiff were obliged to meet the conventional criteria, the Court's function is not to finally adjudicate the issues raised by the respective parties:

> "To justify a temporary injunction it is not necessary that the plaintiff's rights to a final decision, after a trial, be absolutely certain, wholly without doubt; if the other elements are present (i.e., the balance of hardships tips decidedly toward plaintiff) it will ordinarily be enough that the plaintiff has raised questions going to the merits so serious, substantial, difficult and doubtful, as to make them a fair ground for litigation and thus for more deliberative investigation." Hamilton Watch Co. v Benrus Watch Co., 206 F 2d, 738, 740.

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

12. Plaintiff adopts as his own, and by reference incorporates, as grounds for the relief sought, the objections of the Attorney General of the State of New York to the Draft Environmental Impact Statement, as set forth in Appendix K 80-110 of the Environmental Impact Statement.

13. Until the defendants comply with their stipulation that the Risk Assessment Studies will not go forward until there is an environmental impact statement--one addressed to those experiments--this Court should continue the stay in effect, or alternatively preliminarily enjoin those experiments.

Ferdinand J. Mack
17 West Jefferson Street
Suite 106
Rockville, Maryland 20850
Attorney for Plaintiff

CERTIFICATE OF SERVICE

I hereby certify that the foregoing Supplemental Memorandum of Points and Authorities in Support of Motion for Preliminary Injunction and in Opposition to Vacation of Stay and the annexed affidavits of Dr. Stuart Newman and Dr. John C. Cobb were personally served upon the U.S. Attorney for the District of Columbia this 12th day of January, 1978.

Ferdinand J. Mack

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE MARYLAND
20850
301 279-2230

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR., an infant,

Plaintiff

v.

JOSEPH A. CALIFANO, JR., ET AL.,

Defendants

77-916

FILED

JAN 12 1978

JAMES E. DAVEY, Clerk

Civil Action No.

AFFIDAVIT IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER

1. I, Stuart Newman, Ph.D., am an Assistant Professor of Biological Sciences at the State University of New York at Albany, and have held this position for the past two years.

2. I have read and am familiar with a document entitled Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacteria Cells, by M.A. Martin and W.P. Rowe (the "Protocol"), for the conduct of experiments in Building 550 at Ft. Detrick, Maryland.

3. It is proposed by the investigators to manufacture novel organisms in which bacteria (E-coli) closely related to a strain known to colonize the human digestive, urinary, and respiratory tracts will carry and reproduce the genetic information of a virus (polyoma) known to cause cancer in certain species of mammal. These bacteria and their resident plasmids or bacteriophages containing the cancer virus genes will then be introduced by various routes into mice and mouse tissue culture cells. Finally, evidence of productive virus infection in the animals or cells will be assayed.

4. I see several serious hazards associated with the protocol. First, while handling of the recombinant organisms containing polyoma genes is planned to take place under P-4 (highest containment) conditions such facilities are not foolproof: Fort Detrick has had at least one reported mishap under P-4-like conditions in the past. In the case known to me an infectious agent escaped containment as a result of a syringe puncturing a worker's hand through a glove-box glove. Thus, though the chances are minimized, escape from physical containment is possible. The probability increases drastically under the P-2 conditions in which the investigators want to perform their immunologic assays. The switch to minimal containment will depend on demonstrating that heat-treated serum is free of E-coli or bacteriophage lambda. Such a determination is subject to human error and technical failure.

5. Were a recombinant organism to escape physical containment its likelihood of survival will depend on a variety of factors. The E-coli strain to be used (K-12) is not an inhabitant of the normal human intestine, but does survive in germ-free intestines of laboratory animals.

More to the point, strains of E-coli can infect the blood and colonize the pharyax. The degree to which K-12 can do this has not been studied. Considering the more likely of the possible routes of escape under P-4, P-3, and P-2 conditions, this is a grave omission.

6. Once released into the environment recombinant organisms are self-reproducing and cannot be recalled. Even the most debilitated E-coli developed to date can survive for up to eight days in tap water. On lysing,

any bacterium can transfer genetic information to a more robust host. Since bacteria are ubiquitous, the polyoma genes could eventually be disseminated throughout the ecosystem. At present they are limited in their range by the adaptedness of their normal packaging to certain species of mammal.

7. Could polyoma genes harm man or any other organism outside their normal host range? At present virtually nothing is known about the mechanisms by which polyoma and other viruses cause cancer. Most cell biologists suspect that the basic mechanisms are not numerous. Different susceptibilities to a given virus among different species of mammal could represent aspects of recognition that have little to do with the underlying basis of transformation to the cancerous state. When cancer causing genes are reproduced apart from their normal packaging (which after all, is what is recognized by the exposed organism) in hosts which can survive in a wide variety of higher organisms, including man, their carcinogenic effectiveness could be enhanced in those organisms.

8. No details are given on the proposed handling of the "inactivated bacterial lysates". But as the genetic information in this material can be taken up by a wide variety of bacteria, the transfer of this material between laboratories presents a unique hazard to the ecological system.

Stuart A Newman

Kathleen M Pickett

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

77-916

FILED

JAN 12 1978

JAMES E. DAVEY, Clerk

FERDINAND J. MACK, JR., and infact,

Plaintiff

v. Civil Action No._____

JOSEPH A. CALIFANO, JR., ET AL.,

Defendants

AFFIDAVIT IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER

1. I, John C. Cobb, have a Doctor of Medicine degree from Harvard Medical School and a Master of Public Health degree from Johns Hopkins School of Hygiene. I am a Professor in the Department of Preventive Medicine and Comprehensive Health Care at the University of Colorado and have held this position for twelve years. I was Chairman of this Department for six years.

2. I have read and am familiar with a document entitled "Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacterial Cells" by Martin and Rowe (the "Protocol"), for the conduct of experiments in Building 550 at Ft. Detrick, Maryland.

3. According to the introductory paragraphs of the protocol, the proposed experiments are designed to provide information about the "potential benefits and biohazards associated with the production of recombinant DNA molecules." The protocol states the concern on p.2, "...that a negative result may be misinterpreted as indicating that there is little biohazard in DNA recombinant work..." The implication is clear that a positive result would properly be interpreted as indicating that there is a definite biohazard, but a negative result would not rule it out.

4. Evidently, considerable uncertainty about the probable outcome of these experiments results from the fact that these kinds of experiments have never been done; so that past experience is no help. There is evidently no assurance in the minds of the investigators regarding whether the results are likely to be positive or negative; this is shown by the precautions they plan to take.

5. The experiments would attempt to produce a new strain of E. coli with the property of inducing infection acquired by splicing genetic material from mouse polyoma virus.

6. This new strain could escape even from the P-4 facilities and might cause human diseases including cancer.

7. The polyoma virus genes of the new strain of E. coli might, through naturally occurring processes, be transferred to wild type strains ubiquitous in the environment which normally propagate themselves in the guts of animals or humans.

8. This could lead to a widespread epidemic of new animal or human diseases including cancer, many years later,long after the new wild type strain had become widely disseminated.

9. It seems to me short-sighted and self-deceptive to attempt to produce a new cancer-inducing strain of E. coli for the purpose of trying to find out whether or not it can happen, in order to determine whether such experiments are safe. Isn't this asking for trouble?

10. Even if the results were negative, that would give me little comfort. Another slightly different recombinant DNA research project at a later time might still do it, either on purpose or by mistake.

11. In view of the admitted possible hazardous nature of these experiments, and the questionable benefit, it is my opinion that they should not be allowed to proceed until an environmental impact statement has been duly filed under the Environmental Protection Act; so that the public who may be at risk can evaluate the possible risks and benefits before these experiments are undertaken.

John C. Cobb, M.D., M.P.H.

13 June '77
Date

STATE OF COLORADO }
COUNTY OF DENVER } SS.

Personally appeared before me, the undersigned, a Notary Public in and for the State and County aforesaid John C. Cobb, who made oath in due form of law that the foregoing affidavit is true.

WITNESS my hand and notarial seal this 13th day of June, 1977.

Notary Public

Notary Public in and for the State of Colorado, County of Denver.

My Commission Expires: My Commission expires July 24, 1979

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Ferdinand J. Mack, Jr. by and through Mildred A. Mack, Plaintiff,	)	
v.	)	Civil Action No. 77-916
Joseph A. Califano, Jr., et al., Defendants	)	

FILED

JAN 13 1978

JAMES F. DAVEY, Clerk

BRIEF OF THE AMERICAN SOCIETY FOR MICROBIOLOGY AMICUS CURIAE

INTEREST OF AMICUS CURIAE

The American Society for Microbiology (hereinafter referred to as the Society) is a not-for-profit educational organization dedicated to the promotion of scientific knowledge of microbiology and related subjects. This purpose is achieved through a broad range of educational activities including the publication of scientific journals, papers, and symposia and the sponsorship of meetings for the exchang of scientific information.

Underlying the Society's dedication to the advancement of scientific knowledge is its commitment that science serve the public interest. Consequently, the Society has striven through its educational activities to communicate to researchers the proper techniques in developing areas of research. The dissemination of such information assures safe and productive experiments and promotes vigorous research ultimately benefitting the public.

The Society has recognized the need for keeping all interested members of the public informed of new developments in recombinant DNA research. Such hearing of information

by public and private interest groups has been important in light of the special requirements for equipment, containment, and training in carrying out sophisticated experiments. In June of 1977, the Public Affairs Committee of the Society appointed a Recombinant DNA Task Force to study the newly released NIH Guidelines and to make its recommendations concerning them. The six eminent microbiologists appointed to the Task Force were chosen on the basis of their broad expertise in areas of physical and biological containment, microbial genetics, virology, epidemiology, and industrial processes.

Through this task force the Society has served the public and the scientific community as a collector and communicator of objective data on recombinant DNA research. It is similarly for the advancement of the public interest through the communication of objective data that the Society submits this brief.

RECOMBINANT DNA RESEARCH IN ACCORDANCE WITH NIH GUIDELINES, AND THE PROPOSED EXPERIMENT AT FT. DETRICK SPECIFICALLY, PROVIDE IMPORTANT PUBLIC BENEFITS

Prior to addressing the potential environmental impact and public health consequences of recombinant DNA research and the Ft. Detrick experiment, it is appropriate to discuss the public benefits of such research. Even a condensed review of such benefits sets recombinant DNA research in a rational, objective context. Present and potential benefits from recombinant DNA research are multifarious and significant.

Benefits of general recombinant DNA research include applied medical advances; medical and agricultural improvements; and accelerated understanding of the genetic and biochemical basis of disease processes. With respect to the Ft. Detrick test protocol, it is specifically designed to supply a first essential step toward honest risk assessment.

1. Applied Medical Advances

Utilizing recombinant DNA processes, scientists are now able to produce valuable human proteins. Human hormones may be yielded in formerly unavailable quantities thereby significantly improving therapy for certain medical conditions.

For example, a combined effort of research teams at the University of California Medical Center, San Francisco, the City of Hope Medical Center in Los Angeles, and the Salk Institute in LaJolla, has recently resulted in the bacterial production of somatostatin, a hormone naturally produced in the brain. Somatostatin is significant medically because it blocks the production of growth hormones by the pituitary gland and blocks the action of insulin and glucogon. It is important, then, in the treatment of acromegaly--a form of giganticism--and also in the treatment of certain forms of diabetes. By the recombinant DNA technique the quantity of somatostatin produced from 100 gms. of bacteria in 2 gallons of culture medium is equal to the amount previously extracted from 500,000 sheep brains.

Additionally, the isolation of the insulin gene and multiplication of the gene in bacteria is a propitious achievement and an important step in the eventual production of insulin. Thus, the recombinant DNA research has already become a valuable tool in progress against physical illness.

2. Medical and Agricultural Research

Because the development of recombinant DNA research will lead to a fuller understanding of genetic mechansims in complex organisms, scientific discoveries in the aniticpation and prevention of genetic disorders and diseases may result. Similarly, knowledge of genetic processes promises to permit incorporation into the genetic structure of plants valuable traits, such as nitrogen fixation, that will increase food production. 1/

1/ Of course, science has already used genetics to benefit mankind (for example hybrid plants) but with a more complete understanding of the internal cell dynamcis a fuller benefit will become available.

Symbiotic nitrogen fixation involving the mutually beneficial collaboration between root nodule bacteria and clover, vetch, and soybeans, is presently limited to leguminous host plants. Recombinant DNA technology may lead to broader host range with ultimate ability for nitrogen fixation among cereal plants. Higher crop yields at substantially lower cost would be the beneficial result of such advances.

3. Fundamental Scientific Research

Recombinant DNA research will reveal the secrets of the innermost workings of the cell. We will know a great deal more about mechanisms of celular differentation whereby some of the cells of the body form skin, others form muscle or skeletal tissue, and still other aggregate to form highly specialized organs, such as the heart, lungs, spleen, pancreas, etc. We will know more about the controlling mechanisms whereby normal cells become transformed into cancerous cells, whereby some individuals and some tissues are more susceptible to disease than others, and whereby some diseases are inherently genetic in character and are passed from parent to offspring.

The first important data toward understanding regulation and differentiation have now been gathered. It is now possible to obtain highly purified strands of DNA from a variety of bacterial and mammalian cell sources. In order for this kind of work to proceed intelligently, we must have the answers to certain fundamental problems. The polyoma virus experiments proposed for the Ft. Detrick P-4 facility will provide some of these answers.

4. Benefit of the Ft. Detrick Experiment

As explained in the test protocol, the Ft. Detrick experiment will help to determine if such rigid containment as represented by a P-4 laboratory is necessary. If the best

scientists cannot produce a risky organism, then it is reasonable that overly strict containment procedures might be relaxed. Thus the need for sound risk assessment. The Society feels that it would be an abrogation of public responsibility to deny the need for such an assessment.

Two scientific groups in Europe have already conducted initial experiments in risk assessment involving polyoma virus. Tests employing mammalian cell cultures in laboratory glass vessels will soon be started, and studies in experimental animals will begin in a month or two. Meanwhile, any delay of the Ft. Detrick experienced will prevent efforts of American scientific leaders to produce the clear, unequivocal answers that all public spirited persons want and need regarding recombinant DNA research.

RECOMBINANT DNA RESEARCH IN ACCORDANCE WITH THE NIH GUIDELINES, AND THE PROPOSED EXPERIMENT AT FT. DETRICK SPECIFICALLY, WILL NOT HAVE ADVERSE ENVIRONMENTAL OR PUBLIC HEALTH CONSEQUENCES

The weight of scientific opinion now considers recombinant DNA research conducted in accord with the NIH Guidelines to have no adverse environmental or public health consequences. Recent conferences reported in the scientific literature and public media reflect the very broad scientific opinion that such research with E. coli, K12, and its derivatives is safe and has no environmental impact. 2/ Indeed, the Society and other scientific organizations have taken the position, based upon objective work by groups such as the Society's DNA task force, that the present NIH Guidelines are more conservative than necessary and that certain restrictions in the Guidelines could be safely modified.

2/ The specific derivative of K12 to be used at Ft. Detrick is designated Chi 1776.

The Guidelines provide overlapping safeguards of both biological and physical containment. Thus, the recombinant host is a deliberately weakened organism for which the chances of survival outside the laboratory or conversion into a pathogen are negligible. Reinforcing the biological safeguards is the physical containment present in the four tiered laboratory system of the Guidelines.

These safeguards are best described in connection with the specific dangers alleged by plaintiff in the present action. In responding to such allegations, the Society acts not as an adversary to plaintiff. Specific allegations simply provide a concrete setting in which to explain the biological and physical safeguards in recombinant DNA research.

Plaintiff, in the Complaint, Memorandum Supporting the Motion for Temporary Restraining Order, and attached affidavits cites seven dangers to the Ft. Detrick experiment:

> (1) E. coli, the host organism is a ubiguitous organism residing in the human gut. Complaint ¶ 9; Memorandum ¶ 4; Affidavits ¶ 3.

Plaintiff's Complaint and the "expert" affidavits assert that the Ft. Detrick experiment will employ "the bacterium, E. coli, which lives on land and in water all over the earth, and in particular is a common inhabitant of the large intestine of all warm blooded animals, including humans." Affidavits ¶3.

"E. coli", is the name given to a range of over 150 strains of bacteria which have certain characteristics in common. In the numerous different strains, however, there are fundamental differences such as surface molecules, nutrition, growth rate and sensitivity to inhibitors. The differences determine the ability of different strains to survive in different

environments. It is simply not true that the strain of E. coli--namely, Chi 1776--to be used at Ft. Detrick is found in the human gut since, as will be seen, it has been chosen specifically because of its inability to survive in the human gut.

> (2) Although the E. coli , host organism, to be used in the experiment at Ft. Detrick is weakened, it may exchange genetic information with wild strains of E. coli or may survive enough outside a laboratory to cause illness. Affidavits ¶6, 7.

The Society concurs with the defendants that the strain to be used at Ft. Detrick, Chi 1776, "is unable to colonize the human intestinal tract, causes no human or animal disease and presents no threat to the environment." Defs. Memorandum p. 11.

Chi 1776 cannot survive outside of special laboratory conditions and in fact human bile is deadly to the particular strain to be used at Ft. Detrick. The experimental strains of Chi 1776 have been designed for self-destruction outside the laboratory as they require thymine and diaminopimelic acid. There are not enough of these compounds in the general environment to sustain Chi 1776's existence. Consequently, in the outside world they quickly expire. Further, not only is Chi 1776 not a pathogen to man but deliberate attempts to make its progenitor E. coli K12 pathogenic have failed. Moreover, the addition of foreign DNA to a bacterium is likely to decrease rather than increase its chances of survival outside a laboratory.

There is now no reasonable doubt of Chi 1776's safety as a recombinant host. The threat of Chi 1776 being converted into a pathogen and surviving outside the laboratory is virtually impossible. Use of Chi 1776 constitutes the best known biological containment of the recombinant DNA.

> (3) Polyoma virus was first discovered in 1960 and there is insufficient knowledge in the last 17 years of its cancer potential. Affidavit ¶8.

Contrary to the affidavits, the first reports on the polyoma virus were published in 1953, not 1960. Dozens of papers were written and published by a variety of authors in the interim between those two years. 3/ Further, polyoma is widely distributed throughout the environment without evidence of having infected man. The virus is readily isolated from wild mice collected from all over the world and has, interestingly enough, been isolated frequently from wild mice collected in Frederick County, where the plaintiff lives.

Repeated attempts have been made to infect laboratory cell cultures derived from human tissue, and all such attempts have failed to yield virus. Repeated attempts have been made to detect antibodies against polyoma virus in the blood of laboratory workers exposed to the virus. All such attempts have failed. The presence of antibodies in blood samples from human beings is a delicate and sensitive test for human susceptibility to a given agent. The fact that antibodies against polyoma have not been detected in over 300 human blood samples from laboratory workers is impressive evidence that the virus is not dangerous for man.

> (4) A hazard is created that is alive and selfpertpetuating and rapidly reproduces. Affidavit ¶5.

The prospect of E. coli, Chi 1776, surviving outside of the laboratory is negligible. The prospect of Chi 1776 reproducing outside of the laboratory is virtually impossible. Chi 1776 is not selfperpetuating, but rather is a weakened and enfeebled genetic mutant selected by microbiologists especially for its zero hazard qualities. The organism is so inherently delicate that it cannot compete with other native microbial inhabitants of the human or animal intestinal tract. It can only be grown under special laboratory conditions and cannot be "converted" into a pathogen. It just does not have a doomsday potential.

3/ See Attachment A.

(5) Despite precautions, human error is unavoidable and escape will occur. Affidavits ¶4.

The laboratory at Ft. Detrick is a P-4 laboratory by virtue of the extensive safeguards built into its design. The Ft. Detrick protocol provides that all experimental manipulations will be conducted inside closed glass cabinets with insert arms and gloves, through which the researchers will work. Air and water and all physical materials, including glassware, pipettes, cotton stoppers, gauze, inoculating loops and needles, in short, everything that touches experimental biological materials, will be sterilized before leaving the laboratory. So, also, will all biological experimental materials. The controls will be so complete and the physical containment barriers will be so complete that even should there be a "mistake" or "spill" by laboratory workers, it will not create a hazard. Such spill or error would be confined to the interior of barrier equipment, and thus would be a nuisance but not a danger. Finally, the technicians who conduct the individual manipulations will be well trained and under the surveillance of a safety officer. All personnel will know what to do to prevent accidents and what to do should an accident occur.

In order for adverse environmental or health consequences to result from the Ft. Detrick experiment, there would have to occur simultaneously several accidents with the chances of any one occuring already negligible. These events are: (1) a human error that in some unforseeable way permits a recombinant carrying Chi 1776 bacterium to escape a most tightly controlled laboratory in which the organisms are sealed in glass cabinets and the air and water is decontaminated; (2) Chi 1776 bacteria would have to have, in some unforseeable manner, gained survival possibilities outside the laboratory

despite having been designed specifically against such survival; (3) such Chi 1776 would have to have been converted into a pathogen by the addition of DNA from an organism not known to have ever adversely affected man.

> (6) Less than P-4 laboratory protection is to be provided for lysates. Affidavit ¶9.

A lysate results from the deliberate treatment of a bacterial culture with chemicals which kill all of the host cells and release the intracellular DNA, RNA, and protein. It is obvious that such materials are inert and non-infectious and therefore do not require P-4 containment. Furthermore, plasmids cannot transfect E. coli except under very special laboratory conditions which include body temperature, a rapidly growing host cell culture, and high calcium concentration. For all of these reasons it is unreasonable to view lysates as dangerous.

From previous work with polyoma DNA and other kinds of DNA we know that inhalation and ingestion by animals will not produce infection. We also know that laboratory workers have handled DNA from many kinds of infectious viruses for many years without evidence of human infection.

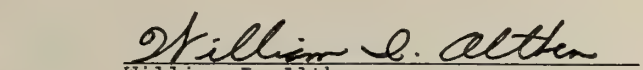
> (7) The Ft. Detrick experiment is a prohibited experiment under present NIH Guidelines. Memorandum ¶7.

This statement is simply wrong and no support for this erroneous contention is given in the plaintiff's "expert" affidavits. Polyoma is not classified as a moderate risk oncogenic virus by the National Cancer Institute, but is classified instead as a low risk oncogenic virus. Only moderate risk agents are excluded by the NIH Guidelines. Indeed, the Guidelines recommend use of polyoma virus as a safe procedure for cloning other molecules.

CONCLUSION

In the opinion of the Society, recombinant DNA research in accordance with the NIH Guidelines and the proposed Ft. Detrick experiment specifically advance the public interest and present no risk of harm to the environment or public health.

Respectfully submitted,



William I. Althen

KILCULLEN, SMITH & HEENAN
1800 M Street, N.W.
Washington, D.C. 20036
(202) 296-5700

Attorney for Amicus Curiae
American Society for Microbiology

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing Brief Amicus Curiae was delivered by hand on January 13, 1978, to Ferdinand J. Mack, Esq., 17 West Jefferson Street, Rockville, Maryland 20850, attorney for plaintiff and to David Schlee, Esq., Assistant United States Attorney, Washington, D.C. attorney for defendant.

William I. Althen

William I. Althen

ONCOGENIC VIRUSES

SECOND EDITION
COMPLETELY REVISED AND ENLARGED

by

LUDWIK GROSS, M.D., F.A.C.P.

Chief, Cancer Research Unit
Veterans Administration Hospital
Bronx, New York

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Isolation of Infectious DNA from Shope Rabbit Papilloma and from SV 40

Ito reported (1960) isolation of infectious DNA from Shope rabbit papilloma, a virus belonging to the same group as the parotid tumor, i.e. polyoma, virus. Furthermore, Ito also observed (1961) that the Shope rabbit papilloma DNA conserves its infectivity after heating to 100°C for 30 minutes. In this respect, therefore, the Shope papilloma DNA is also similar to the polyoma DNA. Isolation of infectious DNA from SV 40 has also been reported (Boiron *et al.*, 1962. Gerber, 1962).

* * *

Attempts to transmit neoplasms with nucleic acid preparations isolated from oncogenic viruses are obviously of considerable interest. They are still, however, in a preliminary phase. Additional studies are needed to clarify this fundamental problem. At least in some of the experiments thus far performed, the possible presence of live residual virus particles in presumably purified nucleic acid extracts has not yet been entirely eliminated. Furthermore, many of such purified nucleic acid extracts have at best only a very slight oncogenic potency.

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ADDENDUM: SKIN TUMORS AND LYMPHOMAS IN HAMSTERS

Graffi and his coworkers inoculated newborn hamsters with normal hamster embryo cell cultures and observed the development in 80 hamsters of multiple wart-like skin tumors originating from hair follicles. Electron microscopic examination revealed in the nuclei of the tumor cells the presence of crystalline arrays of virus particles about 35 mμ in diameter; occasionally, particles were also found in the cytoplasm and in intercellular spaces (GRAFFI, A., SCHRAMM, T., BENDER, E., BIERWOLF, D., and GRAFFI, I., Über einen virushaltigen Hauttumor beim Goldhamster. *Arch. Geschwulstforsch.*, 30: 277–283, 1967). When an attempt was made to transmit these skin tumors by filtrates to newborn hamsters, lymphomas developed in 45 per cent of the inoculated animals; reticulum-cell sarcomas were also induced when centrifuged skin tumor extracts were inoculated into newborn Wistar rats. Electron microscopic examination of the hamster lymphomas revealed in the cytoplasm a small number of spherical virus particles, about 90 to 100 mμ in diameter; some particles were budding from the membrane of the endoplasmic reticulum. The lymphomas induced either in hamsters or in rats could be transmitted by filtrates to newborn hamsters, reproducing the same disease (GRAFFI, A., SCHRAMM, T., BENDER, E., GRAFFI, I., HORN, K.-H., and BIERWOLF, D., Cell-free transmissible leukoses in Syrian hamsters, probably of viral aetiology. *Brit. J. Cancer*, 22: 577–581, 1968).

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. an infant	:	
Plaintiff	:	Civil Action No. 77-0916
v	:	Judge John Lewis Smith, Jr.
JOSEPH A. CALIFANO, JR. et al	:	
Defendants	:	

FILED
JAMES F. DAVEY, Clerk

REQUEST OF PLAINTIFF TO DEFER FOR 30 DAYS DECISION ON PRELIMINARY INJUNCTION AND VACATION OF STAY

Plaintiff respectfully moves the Court to defer for 30 days a ruling on the preliminary injunction sought by plaintiff herein, and the vacation of the stay, sought by defendants herein, upon the following grounds:

1. Counsel for the American Society for Microbiology, intervenor, represented in open Court that the very program of experiments sought to be enjoined in this case has already been conducted in Europe. Counsel also represented to the Court that those experiments have resulted in no known adverse effects from recombinant DNA. The brief of the intervenor indicates that two scientific groups in Europe "have already conducted initial experiments in risk assessment involving polyoma virus." (Brief page 5) Following the arguments before the Court on January 13, 1978, counsel for the intervenor advised counsel for plaintiff that he would provide counsel for plaintiff with the details of the European experiments. This information is highly significant, and ought to be included in the record herein before the Court rules on the pending motions. As soon as counsel for plaintiff learns the source of information about the European experiments, he will endeavor to provide the Court with a more full

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

statement concerning those experiments, for its consideration. If the intervenor's attorney provides plaintiff's attorney with this information promptly, 30 days should be more than adequate to obtain the information, furnish it to the Court and the Court to consider it.

2. Defendants alleged at the hearing before this Court that a weakened K-12 E. coli is to be used, and for that reason, the affidavits filed in support of the motion for a preliminary injunction are defective. They adverted to the fact that a Memorandum of Understanding dated May 23, 1977, spelled out that this weakened strain would be used, and indicated a copy of that Memorandum of Understanding had been furnished to counsel for plaintiff. The file of counsel for plaintiff does not reflect the Memorandum, but if it was furnished to counsel for plaintiff, it would have been delivered to the persons who signed affidavits, which have been filed by plaintiff. Counsel for plaintiff is circulating to his affiants, Exhibit #2, the Memorandum of Understanding of May 23, 1977, to ascertain whether that Memorandum in any way alters the opinions set forth in the affidavits filed herein. Those affiants may already have considered use of the weakened strain, spelled out in the Memorandum, and in that event, the defendants' argument would have no weight. The same would be true if, upon consideration of the Memorandum, affiants reiterate their previously held opinions. On the other hand, if the affiants change their opinions based upon the Memorandum of Understanding, that fact should, and will, be made known to the Court. For these reasons, the Court should defer its decision in this matter for 30 days, to permit the Memorandum of Understanding of May 23, 1977, to be circulated among plaintiff's affiants.

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

3. At the hearing before this Court on January 13, 1978, the Court inquired of counsel for plaintiff what he considered the function of the Environment Protection Agency to be. It seemed (perhaps erroneously) to counsel for plaintiff that the Court was suggesting that, EPA having voiced no objection to the Frederick experiments, that the matter had been considered and approved. This is not the case.

The response of EPA to the draft Environmental Impact Statement is contained at Appendix K-158, et seq., of the Appendix to the Environmental Impact Statement. It must be borne in mind that at no place in the draft Environmental Impact Statement or the Guidelines was EPA advised of the intention of defendants to conduct the Risk Assessment Studies at Frederick. EPA was not advised of defendants' intentions to deliberately create a bio-hazard at Frederick. In addition, the objections of EPA as set forth in its response to the draft Environmental Impact Statement, hardly constitute warm endorsement by that agency. EPA rated the Environmental Impact Statement as "ER-2." (Appendix K-160 to Environmental Impact Statement) This rating indicates that:

> "EPA has reservations concerning the environmental effects of certain aspects of the proposed action. EPA believes that further study of suggested alternatives or modifications is required and has asked the originating Federal agency to reassess these aspects.
>
> ....
>
> Category 2--insufficient information
>
> EPA believes that the draft impact statement does not contain sufficient information to assess fully the environmental impact of the proposed project or action. However, from the information submitted, the agency

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 100
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850
301 279-2230

> is able to make a preliminary determination of the impact on the environment. EPA has requested that the originator provide the information that was not concluded in the draft statement." (Appendix K-165 to Environmental Impact Statement)

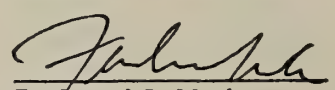
4. Subsequent to dictating the foregoing, counsel for plaintiff ascertained from the Court reporter that the representations to the Court by the intervenor's attorney on January 13, 1978, were as follows:

> Mr. Althen: In Europe this precise experiment has already been run. This experiment has already been conducted in Europe.
>
> The Court: With what consequences in Europe?
>
> Mr. Althen: With no adverse consequences and that was a short time ago in Europe. And we recognize the plaintiff cites long-term consequences but there have been no escapes, no injury from that European experiment and European studies are now proceeding.

Inquiry by counsel for plaintiff of Mr. Althen in the hall following the hearing, revealed that the foregoing representations are not accurate. Mr. Althen advised counsel for plaintiff that he had not heard one way or another as to whether there had or had not been any adverse consequences from those European experiments. While perhaps not intentional, the significance of the mis-representations to this Court is such that the record must be corrected before the Court makes a decision in this matter.

The issues in this case are sufficiently important that the Court should defer its decision for 30 days.

Respectfully submitted



Ferdinand J. Mack
17 West Jefferson Street, Suite 106
Rockville, Maryland 20850
Attorney for Plaintiff

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

CERTIFICATE OF MAILING

I hereby certify that a copy of the foregoing was mailed, postage prepaid this 16th day of January 1978, to David Schlee, Assistant U.S. Attorney, U.S. District Courthouse, Room 3438B, Washington, D.C. 20001 and to William I. Althen, 1800 M Street, N.W., Washington, D.C. Attorney for the American Society for Microbiology.

Ferdinand J. Mack

ERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
WEST JEFFERSON ST.
CKVILLE, MARYLAND
20850

301 279-2230

Ferdinand J. Mack
Attorney At Law
Suite 106 Old Town Center
17 West Jefferson Street
Rockville, Maryland 20850
301 279-2230

Frederick Office:
Airport Terminal Building
Frederick, Maryland 21701
301 694-8666

January 19, 1978

Attachment
CA 77-0916

FILED
JAN 16 1978
JAMES R. BRADY, Clerk

William I. Althen, Esquire
1800 M Street, N.W.
Washington, D.C.

Dear Mr. Althen:

This is to confirm the understanding we had when we left the Court on Friday, January 13, 1978, that you will, as soon as possible, advise me of the source of the information relating to the European experiments involving Risk Assessment Studies, and any other details that you have concerning those experiments. As you can see from the enclosed pleading, time is quite important.

Very truly yours,

FERDINAND J. MACK

Enclosure

FJM/lh

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, Jr. Plaintiff, v. JOSEPH A. CALIFANO, Jr., et al., Defendants.	)	Civil Action No. 77-916

FILED

JAN 20 1978

JAMES F. DAVEY, Clerk

MEMORANDUM IN OPPOSITION TO PLAINTIFF'S REQUEST TO DEFER FOR 30 DAYS

Plaintiff has moved the Court for a 30-day extension of time to submit additional information. In effect, plaintiff asks the Court to enter a 30-day preliminary injunction without having to meet any of the requirements for a preliminary injunction. For the reasons discussed below, plaintiff's motion should be denied.

First, plaintiff in essence asks the Court to enter a preliminary injunction for 30 days. Such an injunction must be accompanied by the normal proof of probable success on the merits, probability of irreparable harm, and general public interest. As indicated in our Opposition to Plaintiff's Original Motion for a Preliminary Injunction (hereinafter "Def. Opp."), filed December 30, 1977, plaintiff has made no such showing. Nothing in plaintiff's new papers indicate any additional reasons as to why plaintiff should be given preliminary injunctive relief. Indeed, we know of no authority for the Court to preliminarily enjoin for 30 days without plaintiff

meeting his full burden of proof. The Rules specifically provide that Temporary Restraining Orders are limited to ten-day's duration, unless extended or consented to. F.R. Civ.P. 65(b).

Second, plaintiff has had ample opportunity to submit all relevant information and affidavits prior to the hearing held on January 13, 1978. This suit was filed in May 1977, and notice of the filing of the environmental impact statement was given on November 29, 1977. Both before and after the suit was filed defendants have voluntarily supplied information to plaintiff concerning the experiment. Plaintiff sought no formal discovery. It is now much too late to seek additional time to delay this experiment.

Third, it is important to begin this experiment as promptly as possible since NIH hopes to gain important additional information concerning recombinant DNA technology. See Def. Opp. at 13-14; Nutter Aff. NIH is prepared to begin the experiment in the next two weeks, and further delay as sought by plaintiff here is unwarranted.

Fourth, plaintiff and his experts should have known throughout these proceedings that a "weakened strain" of E. coli K-12 was to be used. Both the environmental impact statement and defendant's opposition to plaintiff's motion for preliminary injunction indicated at length the properties of EK2 host-vector systems and that EK2 systems would be used in the experiment.

Plaintiff's apparent assumption that unmodified E. coli would be used is inexcusable.

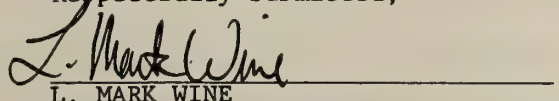
Fifth, plaintiff's discussion on pages 3 and 4 of his latest motion to delay suggests that EPA has been critical of the experiment. This implication is untrue. EPA's comments on the draft environmental impact statement are totally irrelevant since the draft EIS has been extensively revised and rewritten, partly in response to public and agency comment. Significantly, plaintiff did not comment on the draft EIS. See EIS, App. K.

Finally, plaintiff's generalized affidavits are simply insufficient to establish any probability of irreparable injury. At best, the affidavits reveal general speculation that the experiment might accidently result in some materials escaping from the laboratory and that such materials might be harmful. None of these affidavits deal specifically with the provisions of the Guidelines or the discussion in the EIS, both of which have undergone extensive scientific and public environmental review. Plaintiff's burden is to prove that there is a reasonable probability of irreparable injury; mere speculation is insufficient. Plaintiff's submissions are woefully inadequate to justify an injunction. Plaintiff's request for 30 more days to gather new information is similarly based merely on speculation and should be denied.

Conclusion

It is now time to get this matter out of the courts and into the research laboratory without further delay. Plaintiff's extraordinary request for additional time should be denied.

Respectfully submitted,



L. MARK WINE
Land and Natural Resources Division
Department of Justice
Washington, D. C. 20530
(202) 739-2712

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that I have served copies of the foregoing Memorandum in Opposition to Plaintiff's Request to Defer for 30 Days, and Order, upon the below-listed addressees on this 19th day of January 1978:

Ferdinand Mack, Esquire
17 West Jefferson Street
Rockville, Maryland 20850

William I. Althen, Esquire
Kilcullen, Smith and Heenan
1800 M Street, N. W.
Washington, D. C. 20036

L. MARK WINE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. an infant, Plaintiff,	)	
v.	)	Civil Action No. 77-0916
JOSEPH A. CALIFANO, JR. et al. Defendants.	)	

FILED
JAN 20 1978
JAMES F. DAVEY, Clerk

SUPPLEMENTAL MEMORANDUM

Pursuant to the request of Plaintiff, amicus curiae, American Society for Microbiology, by and through its undersigned counsel, hereby informs Plaintiff that the source of information on European experiments concerning recombinant DNA research was an open meeting of the Advisory Committee to the Director of the National Institutes of Health held on December 15 and 16, 1977. Particular reference is made to the testimony of Dr. John Tooze, European Molecular Biology Organization, Post Fach 1022.40, 6900 Heidelberg, West Germany. Although the formal proceedings of such meeting have not been published, members of amicus curiae who were in attendance have reported that Dr. Tooze informed the meeting of European recombinant DNA experiments involving polyoma virus comparable to the proposed Ft Detrick experiment except, we understand, that containment procedures were not as tightly controlled as the P-4 laboratory at Ft Detrick.

Because of the late date at which amicus curiae became aware of the instant action, amicus curiae had only one week to prepare its amicus brief. Therefore, although counsel for the amicus curiae regrets any mistaken impressions that Plaintiff's counsel may have received from a conversation in the elevator while

leaving the courthouse, amicus curiae is pleased with the opportunity to present this additional information to the Court.

Respectfully submitted,

William I. Althen

William I. Althen

Kilcullen, Smith & Heenan
1800 "M" Street, N.W.
Suite 600N
Washington, D.C. 20036
Tel. (202) 296-5700

Attorney for Amicus Curiae
American Society for Microbiology

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing Supplemental Memorandum was mailed by first class mail, postage prepaid, this 19th. day of January 1978 to Ferdinand Mack, Esquire, Senate 106, 17 West Jefferson Street, Rockville, Maryland 20850, Attorney for Plaintiff, and Mark Wine, Esquire, Room 2136, Land and Natural Resources Division, Department of Justice, Washington, D.C. , Attorney for Defendants.

William I. Althen

C.A. 77-916

January 12, 1978

FILED

JAN 23 1978

JAMES F. DAVEY, Clerk

The Honorable Judge John Lewis Smith, Jr.
U.S. District Court for the District of Columbia
Washington, D.C. 20001

RE: Civil Case No. 77-0916;
Ferdinand J. Mack, Jr. vs. Joseph A. Califano, Jr. et al.

YOUR HONOR:

I am Dr. Naum S. Bers, a bio-medical engineer from Rockville, Maryland, well qualified and certified for the administrative management of safety in bio-medical laboratories of high containment research facilities, such as those at Ft. Detrick, in Frederick, Maryland. Accordingly, I am well aware of the record of Court in the above referred to case, and its latest entries have prompted me to write this letter which I wish, respectfully, to be regarded as an expression of my views and recommendations for your consideration, as follows:

In my confirmed opinion, no adequate data base has been available to the authors of the NIH Guidelines for Recombinant DNA Research ... so as to establish with any desired probabilistic confidence what might be prudent controls and proper levels of containment for the "permitted experiments" under those Guidelines. To correct for that deficiency, NIH officials have been advised to generate an Intramural Risk Assessment Program/Plan of "special experiments" for which, if necessary, the NIH Director may even grant some justified exemptions, under very strict controls.

Unfortunately, however, no such Risk Assessment Program/Plan has been generated yet ... to say nothing of an Environmental Impact Statement (EIS) that would be required for it under the Nat'l Envir'l Protection Act (NEPA).

I sympathize with the "special interest", which is, to accelerate the present course of some potentially rewarding genetic research investigations through the use of some potentially hazardous recombinant DNA's. Using such technique, one may be able to first separate and then recombine some specific bacterial genes and viral genes ... and then clone such hybrid combinations in bacteria ... and so obtain, much cheaper and much faster, enormous amounts of special test material for experiments with very many test animals. However, such an abundance of hybrid microorganisms poses potential hazards, of yet unknown extent, to laboratory workers, the general public, and the environment.

In conclusion, I believe that a comprehensive Risk Assessment Program is needed to focus on obtaining safety data from every stage of design and use of this "technique and vehicle of accelerated genetic research". To ensure investigators' facility and commitment to such tasks and goals, I believe that a proper Environmental Impact Statement must include an indication that the NIH Director has taken into serious consideration the impacts (on his laboratory workers, the general public, and the environment) of those proposed experiments, through statements of special duties and responsibilities assigned to a Safety Officer and a Safety Manager, each designated distinctively for both full time work on such intramural NIH actions and as models for control of such funded extramural NIH tasks. To this effect, I have made several written recommendations to the NIH Director and, upon request, I would be happy to provide the Court with copies of all my correspondence with NIH officials on this matter.

Finally, I believe that it might be in the best interest of the general public, as well as my own, to have this letter red in Court, thus transmitting its contents simultaneously to both sides of this case.
Thank you.

Respectfully submitted,

Naum S. Bers

Naum S. Bers, Ph.D.
P.O. Box 1692
Rockville, Maryland 20850

C.A. 77-916

January 23, 1978

The Honorable Judge John Lewis Smith, Jr.
U.S. District Court for the District of Columbia
Washington, D.C. 20001

FILED
JAN 23 1978
JAMES F. DAVEY, Clerk

RE: Civil Case No. 77-0916;
Ferdinand J. Mack, Jr. vs. Joseph A. Califano, Jr. et al.

YOUR HONOR:

In keeping with my comments of concern, as related in my letter to you of January 12, 1978, and as expressed in open Court on January 13, 1978, I, Naum S. Bers, am prompted respectfully, once again, to hereby express my concern over ... still another deceiving entry in the record of Court by seemingly misinformed attorneys for the defendants in this case.

As you know, at first, I was prompted by an entry of December 30, 1977, in which attorneys for the defendants quoted from a Supreme Court decision that ... "THE ONLY ROLE FOR A COURT IS TO ENSURE THAT AN AGENCY HAS TAKEN A "HARD LOOK" AT THE ENVIRONMENTAL CONSEQUENCES OF ITS ACTIONS." ... My comment in open Court to that quotation was that NO SUCH "HARD LOOK" MAY BE CLAIMED BY THE DEFENDANTS SINCE NEITHER PRESENT NIH GUIDELINES NOR THEIR PRESENT ENVIRONMENTAL IMPACT STATEMENT EVEN MENTION SUCH ESSENTIAL SAFETY "HARD LOOKERS" AS A SAFETY MANAGER AND A SAFETY OFFICER.

Now, suddenly, in their entry of January 17, 1978, the defendants' latest group of attorneys state that ... "THE TECHNICIANS WHO CONDUCT THE INDIVIDUAL MANIPULATIONS WILL BE WELL TRAINED AND UNDER THE SURVEILLANCE OF A "SAFETY OFFICER" ... The fact remains, however, that NO SUCH POSITION OF RESPONSIBILITY HAS BEEN INCLUDED YET IN EITHER THE NIH GUIDELINES OR IN THEIR ENVIRONMENTAL IMPACT STATEMENT ... TO SAY NOTHING ABOUT THE STILL UNFULFILLED NIH REQUIREMENT FOR THE APPOINTMENT OF A SAFETY MANAGER OVER THEIR HIGH CONTAINMENT FACILITIES AT FT. DETRICK, IN FREDERICK, MARYLAND.

Respectfully submitted,

Naum S. Bers

Naum S. Bers, Ph.D.
P.O. Box 1692
Rockville, Maryland 20850

C.A. 77-0916

January 27, 1978

The Honorable Judge John Lewis Smith, Jr.
U.S. District Court for the District of Columbia
Washington, D.C. 20001

FILED
JAN 30 1978
JAMES E. DAVEY, Clerk

RE: Civil Case No. 77-0916;
Ferdinand J. Mack, Jr. vs. Joseph A. Califano, Jr. et al.

YOUR HONOR:

Please regard this information for becoming supplementary to my letter of January 23, 1978, through which I have expressed my concern over what I termed ... "still another deceiving entry in the record of Court" ... by ... "the defendants' latest group of attorneys" ... as follows:

The above referred to deceiving entry is contained in a document "filed" on January 13, 1978. It became known to me on January 17, 1978, when it was entered into the files which are available to the general public. The author of that document is Mr. William I. Althen, an attorney with Kilcullen, Smith & Heenan, and a so-called "amicus Curiae" attorney of the American Society for Microbiology. On page 9 of that document, called "Brief of the American Society for Microbiology Amicus Curiae", I found the deceiving entry which states that ... "THE TECHNICIANS WHO CONDUCT THE INDIVIDUAL MANIPULATIONS WILL BE WELL TRAINED AND UNDER THE SURVEILLANCE OF A "SAFETY OFFICER" ...

As stated in my letter of January 23, 1978, the above referred to entry is deceitful because ... THE "SAFETY OFFICER" POSITION OF RESPONSIBILITY HAS NOT BEEN INCLUDED YET IN EITHER THE NIH GUIDELINES OR IN THEIR ENVIRONMENTAL IMPACT STATEMENT ... TO SAY NOTHING ABOUT THE STILL UNFULFILLED NIH REQUIREMENT FOR THE APPOINTMENT OF A "SAFETY MANAGER" OVER THEIR HIGH CONTAINMENT FACILITIES AT FT. DETRICK, IN FREDERICK, MARYLAND.

Respectfully submitted,

Naum S. Bers

Naum S. Bers, Ph.D.
P.O. Box 1692
Rockville, Maryland 20850

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR.
an infant

Plaintiff

v

JOSEPH A. CALIFANO, JR. et al

Defendants

Civil Action No. 77-0916

FILED
FEB - 6 1978
JAMES F. DAVEY, Clerk

SUPPLEMENTAL MEMORANDUM OF PLAINTIFF

This memorandum is directed to the two matters that counsel for plaintiff requested additional time to address.

First is the representation of counsel for the intervenor, made in open court, that the Risk Assessment Studies, the subject of this action, have already been run in Europe "with no adverse consequences." The Government has furnished counsel for plaintiff with that portion of the transcript of proceeding upon which counsel for the intervenor claims he based that representation to the court. At no point in the transcript is the statement of counsel for the intervenor that there have been "no adverse consequences" confirmed. It is, as counsel for the intervenor advised counsel for plaintiff following the last court hearing, true only that no one has heard one way or the other as to whether there have been any adverse consequences from the European Risk Assessment Studies.

The second matter as to which counsel for plaintiff wished to address the court was the question of whether the particular organisms which were to be utilized in the Risk Assessment Studies were in fact considered

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850
301 279-2230

by the affiants who supplied affidavits in support of plaintiff's motion for a preliminary injunction. Four of those five affiants have replied, and annexed hereto are their affidavits, confirming that the opinions they have previously expressed are predicated upon utilization by the defendants of the organisms described in IMUA-18 and the Statement of Understanding and Agreement of May 23, 1977. Their comments on the hazards of the Risk Assessment Studies thus remain unimpeached.

Ferdinand J Mack
17 West Jefferson Street
Suite 106
Rockville, Maryland 20850
Attorney for Plaintiff

CERTIFICATE OF MAILING

I hereby certify that a copy of the foregoing Supplemental Memorandum of Plaintiff and affidavits were mailed, postage prepaid this 3rd day of February, 1978 to Toby Kaczensky, Assistant United States Attorney, U.S. District Courthouse, Room 3438-B, Washington, D.C. 20001, L. Mark Wine, Esquire, Land and Natural Resources Division, Department of Justice, 10th and Constitution, N.W., Washington, D C. 20530 (Room 2136) and to William Althen, Esquire, 1800 M. Street, N.W., Washington, D.C.

Ferdinand J. Mack

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

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JAMES F. DAVEY, Clerk

SUPPLEMENTAL AFFIDAVIT OF RUTH HUBBARD IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION

I Ruth Hubbard being first duly sworn state as follows:

I have read and am familiar with the document entitled IMUA-18, and the statement of understanding and agreement dated May 23, 1977. The opinions expressed by me in my previous affidavit filed in this case are unchanged. At the time those opinions were expressed, I was familiar with the E. coli which this document indicates will be utilized for the Ft. Detrick experiments.

As set forth in the attached memorandum of Drs. Goldstein, Orego and Youderian to Donald S. Frederickson, Director, National Institutes of Health, dated May 30, 1976, the viability of enfeebled strains of E. coli in the presence of foreign DNA remains, and will remain, unknown until the DNA is inserted into the organism. Preliminary published experiments already show that viability can be altered when foreign DNA is inserted into E. coli.

Ruth Hubbard

Ruth Hubbard

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

STATE OF MASSACHUSETTS)
) ss:
COUNTY OF Middlesex)

I HEREBY CERTIFY that before me, a Notary Public, in and for the State and County aforesaid, personally appeared Ruth Hubbard and acknowledged the foregoing Supplemental Affidavit to be her voluntary act and deed.

WITNESS my hand and notarial seal this 25th day of January, 1978.

R E James Hunter
Notary Public

My Commission expires December 31, 1982

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

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ANALYSIS AND CRITIQUE OF THE CURTISS REPORT ON THE *ESCHERICHIA COLI* STRAIN INTENDED FOR BIOLOGICAL CONTAINMENT IN DNA IMPLANTATION RESEARCH

Richard Goldstein*
Christian Orrego †
Philip Youderian §

Boston Area Recombinant DNA Group

* R.G. - Dept. of Microbiology & Molecular Genetics
Harvard Medical School

† C.O. - Rosenstiel Basic Medical Sciences Center
Brandeis University

§ P.Y. - Dept. of Biological Sciences
Massachusetts Institute of Technology

submitted to the NIH Recombinant DNA Molecule Program Advisory Committee

May 30, 1976

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Attachment
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I. SUMMARY AND CONCLUSIONS

The proposed candidate strain χ1776 (and its plasmid containing equivalent, χ1876) do not satisfy the criteria for EK-2 status outlined in the "Proposed Guidelines for Research Involving Recombinant DNA Molecules," (January 1976) (see this paper, Section III).

First, as Curtiss et al. state, "there is no available plasmid cloning vector which has been specially constructed for safety and/or which is dependent on χ1776 or some other suppressor-containing strain for its replication" (Curtiss et al., p.3).

Second, and most important, the data presented by Curtiss concerning the survival of χ1776 (or χ1876) do not and can not promise the reduced survival of the same strain carrying a cloned foreign DNA sequence. Experiments performed by Dr. Ronald W. Davis (personal communication) have demonstrated that cloned DNA from a eukaryotic organism (*Saccharomyces cerevisiae*) can correct for genotypic defects of *Escherichia coli*, such as auxotrophy for histidine biosynthetic pathway genes or recombination deficiency (recA).

Third, the proposed strains have not been tested in any natural environment (environment not specifically peculiar to the laboratory), with the exception of the rat gastrointestinal tract. In distilled or tap water, the strains show identical survival kinetics with their prototrophic parent. Environments not tested include the human gastrointestinal tract, raw sewage, and soils, to which the strain may have easy access (see this paper, §B22).

Fourth, the strain χ1876 produces pSC101-containing minicells

(1-2 per cell) which are capable of surviving under conditions that the mother cells cannot. The capability of these minicells to disseminate genetic information to other cells was not extensively tested, nor was a detailed study of the survival of this capability performed. Minicells are known to act as genetic donors, as well as recipients, during conjugational processes (Frazer and Curtiss, 1975) (see this paper, §§A11c, B25).

Fifth, the strain survives better in minimal environments* than in rich ones lacking the growth factors required for viability*. This would allow for dissemination in famine environments, such as drains, without appreciable death, and rapid exchange of genetic information in suddenly richer environments, such as sewers (see this paper, §§A8a, A12a, A12b, A13, B22, B26).

Sixth, the introduction of the pSC101 plasmid vector into χ1776 allows it to survive much longer under certain conditions than χ1776 alone. This is the first evidence obtained on the effects of introducing additional DNA into χ1776 upon its survival. The result is that introduction of this particular additional DNA into χ1776 increases its possibilities for survival. It should be noted that in none of the cases tested, does χ1876 survive <u>less</u> well than χ1776, under the identical sets of conditions (see this paper, §§A10c, A12a, A12b, A13, A14c, A18, A19, A20).

---

* By "minimal environments" we denote either BSG (buffered saline with gelatin), tap water, or distilled water.

By "rich [environments] lacking the growth factors required for viability" we denote that class of media lacking either thymidine/thymine or DAP, such as L broth + thymidine, ML + casamino acids + thymidine, biotin,

Seventh, it is not clear how well χ1876 dies in the presence of other bacteria in a rich environment lacking the growth factors required for viability**, since in the direct measurement of death rate, the conclusion that χ1876 dies rapidly in the presence of χ289 is based upon a single datum-point. This rate of death does not agree with the rate of plasmid transfer observed in conjugation experiments performed under the same physiological conditions, assuming that conjugational transfer is limited by viability. Furthermore, the extent to which phenotypic rescue by other bacteria of the death of χ1876 in a rich environment lacking the growth factors required for viability is due to cross-feeding is not measured (see this paper, §§A8c, A9b, A9c, B26).

Eighth, the ability of χ1776/χ1876 to transfer genetic information by known resistance (R) factor transfer systems is reduced only by one-hundred fold at best at at least one of the two temperatures, 32°C and 37°C, for the vast majority of cases, when compared to the unweakened parent (see this paper, §§A15, A16, A17, A18, A19, A20, A21, B25, B28, B29).

Ninth, since markers are frequently lost during routine manipulations of a complex auxotroph, especially those markers detrimental to the survival of *Escherichia coli* (see this paper §B24), it is not certain how handling of χ1776/χ1876 by many laboratories will alter the genotypic and phenotypic properties of this strain. How dispensation and use of any EK-2 candidate system will alter the genotypic and/or phenotypic properties of the system must be assessed prior to certification.

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and glc (glycerol or glucose ?). We cite other internal references that might bear on this point, such as the survival of χ1776/χ1876 during drying conditions (§A13, Curtiss et al., Figure 2B).

** See Curtiss et al., Figure 16.

We recommend that the construction and testing of possibly suitable EK-2 host/vector systems, continue with careful and extensive experimentation, along lines that reconcile the objections we have raised in this critique. Time must be allowed in the construction of an EK-2 host so that sacrifices in the construction (such as that of the isogenicity of χ1776 with its parent and the direct use of nitrous acid mutagenesis) are not made in the future for the sake of expediency (see this paper §§A1, A2, A3, A4, A5, A6, A7).

We commend the honesty and candid nature with which Roy Curtiss' group has presented their results, and hope that their very impressive experimental efforts and frank presentation will serve as examples for other groups attempting to develop similar EK-2 systems. It is with a deep sense of admiration for the work of Dr. Roy Curtiss III and his eight co-workers at the University of Alabama that we offer our detailed criticisms, the highest form of respect that one group of scientists can pay to another group of scientists.

At present, we find that the "weakened" *Escherichia coli* strains obtained by the Curtiss group have many "strengths" which do not support the concept of biological containment.

II. INTRODUCTION

The NIH Guidelines for Research Involving Recombinant DNA Molecules will seek to contain bacterial hosts and/or viruses carrying implanted foreign genes by assigning combinations of different levels of physical and biological containment depending on the specific types of experiments to be performed. The term biological containment refers to the use of genetically modified or "disarmed" strains of the human gut bacterium *Escherichia coli* as host for the propogation of foreign genes. To quote the Proposed Guidelines approved by the NIH Recombinant DNA Molecule Program Advisory Committee, the disarmed strain of *Escherichia coli* K12 "... should not permit survival of the cloned DNA fragment in other than especially designed and carefully regulated laboratory environments at a frequency greater than 10^{-8}." This strain of *E. coli* will be designated EK-2 and its use as host to carry implanted DNA fulfills the EK-2 level of biological containment.

Dr. Roy Curtiss III and eight co-workers at the University of Alabama have worked toward the construction of such an EK-2 strain for more than a year and their data were presented to the NIH Recombinant DNA Molecule Program Advisory Committee at its most recent meeting two months ago. Curtiss et al. (1976) have summarized their efforts and achievements: "... a total of 13 genetic manipulations (were required) to obtain a strain that should meet the requirements of an EK-2 host as specified in the current proposed NIH Guidelines for Recombinant DNA Molecule Research. This strain cannot synthesize the murein layer of its cell wall under other than carefully controlled laboratory conditions due to two mutations at different map (chromosomal) positions, is unable

to synthesize the mucopolysaccharide colanic acid which can facilitate the ability of *E. coli* to survive in the absence of the murein layer of the cell wall, is sensitive to bile salts and detergents, undergoes thymineless death and degrades its DNA in environments lacking thymine or thymidine, is resistant to a number of *E. coli* transducing phages, is very sensitive to ultraviolet light irradiation, is unable to act as a recipient in matings with donors possessing conjugative plasmids in five of the groups commonly or occasionally found in enteric microorganisms and is defective as a recipient in matings with donors possessing other conjugative plasmid types."

The present report contains an analysis and critique of the EK-2 strain proposed by Curtiss and co-workers as described in their paper "Construction, Properties and Testing of χ1776." The summary and conclusions presented in Section I of this report as well as the following comparison of the properties of χ1776/χ1876 with the NIH Provisional Guidelines specifications for an EK-2 host have been prepared in order to make our criticisms directly accessible to those unfamiliar with the terms and concepts used in the technical analysis, which we present in a separate section (Section IV).

III. COMPARISON OF NIH GUIDELINES SPECIFICATIONS FOR EK-2 HOST TO THE PROPERTIES OF χ1776 AND χ1876

It is of interest to compare the EK-2 specifications called for in the Provisional NIH Guidelines (1976) to what has been possible for the Curtiss group to achieve in the construction of χ1776 and χ1876. The latter strain (χ1876) is the designation for χ1776 carrying the pSC101 plasmid (the "vector" for gene implantation), which confers resistance of the bacterium toward the antibiotic, tetracycline. The comparison made below does not imply an agreement with the contents of the NIH Guidelines (for our detailed critique of the Guidelines, see reference 2), rather it is illustrative of the biological obstacles that are being encountered in realizing "biological containment" for *Escherichia coli*.

Provisional NIH Guidelines:	χ1776 and χ1876:
"... modifications of the *E. coli* K12 host and/or plasmid or phage vector should not permit survival of the cloned DNA fragment† in other than specifically designed and carefully regulated laboratory environments..." (Guidelines, p. 18)	Curtiss et al. point out: "In testing χ1776, we have not satisfied these criteria because that was not possible and because we now believe there are some flaws in the above stated requirements for an EK-2 system." (Curtiss et al., p. 3) The strains proposed would have EK-2 status based on survival of the host without a cloned DNA in them. The authors point out "... one could choose a diversity of cloned DNA fragments some of which might increase the host's and/or vector's potentials for survival and/or transmission of DNA and others which would decrease these potentials and therefore create a false sense of safety." (Curtiss et al., p.3) This last statement voices a concern shared by a number of scientists, namely, that the presence of a foreign

† All underscorings in this Section are ours.

Provisional NIH Guidelines:	χ1776 and χ1876:
	DNA in the bacterial cell will alter its physiological properties. Credence for this argument emerges from some of the comparative survival data between χ1776 and χ1876, which indicate that the presence of additional DNA in the form of the pSC101 plasmid does change, and sometimes quite radically, the properties of the cell (see Curtiss et al., Figures 11 and 22, p. 21, and this paper, Section I, second point, §§10b, 10c, 10d, 14d).
"In testing the level of biological containment afforded by a proposed EK-2 plasmid-host system, it is important to design relevant tests to evaluate survival of the cloned DNA under conditions that are possible in nature and that are also most advantageous for its perpetuation." (Guidelines, p.20)	The above has not been achieved as indicated previously by Curtiss and co-workers. Also, the tests that have been performed on the "disarmed" strains do not contemplate a variety of conditions possible in nature and in the laboratory (see this paper, Section IV-B).
"Survival of the cloned marker by transduction could also be evaluated by introducing a known generalized transducing phage into the system." (Guidelines, p.20)	This experiment is not reported. This test is of importance given that the authors obtain multiplication of the *E. coli* virus T6 upon infection of χ1776 under starvation conditions. Furthermore, virus growth is more prolific in the most deprived medium tested (Curtiss et al., Figures 29 and 30, see this paper, §§20a and 20b).
"It would be useful to determine the survival of the host under non-growth conditions such as in water and as a function of drying time after a culture has been spilled on a lab bench." (Guidelines, p.21)	Survival of these strains was tested under the above conditions but was observed to be no different than the survival of their non-weakened parent under drying conditions (Curtiss et al., Figure 28). A very large number of cells (0.1 to 1.0% of the initial concentration of cells) were able to retain viability up to 8 days in tap water (Curtiss et al., Figures 25, 26, and 27, see this paper, §§12 and 13).

Provisional NIH Guidelines:	χ1776 and χ1876:
"The combination of the dapD8, deletion bioH-asd and deletion gal-chl^{r} mutations in *E. coli* K12 results in no detectable survivors in feces of rats following feeding by stomach tube of 10^{10} cells in milk and similarly leads to complete lysis of culture suspended in broth medium lacking diaminopimelic acid (DAP)." (Guidelines, p.19)	The fate of stomach tube fed cells is confirmed (Curtiss et al., Table 17), although there are questions as to the statistical validity of these data, as the sample size is very small (only 3 to 9 rats per sample average, see this paper, §14a). Nevertheless, in the case of χ1876 (the complete host-vector system), survival upon passage through the rat gut occurs when the antibiotic tetracycline is administered concurrently with the feeding of cells. Tetracycline appears to "override" all the "safety" properties of the strain (Curtiss et al., Table 17, see this paper, §§14a, 14b, and 14c). On the other hand, complete lysis of a culture suspended in a minimal medium lacking DAP does not occur (Curtiss et al., Figure 22). In fact, one million cells (1% of the total initial cells) are able to survive 180 hours of DAP starvation. This experiment demonstrates that the presence of the pSC101 plasmid in χ1876 allows an enormous survival advantage over the strain without the plasmid in very poor media. This particular experiment can be considered one of the ultimate tests of biological containment, since survival of χ1876 is tested in poor media lacking both DAP and thymine (see this paper, §§10a, 10b, 10c, and 10d).
"Mutations can also be introduced into the plasmid to cause it to be dependent on a specific host, to make its replication thermosensitive and/or to endow it with a killer capability such that all cells (other than its host) into which it might be transferred will not survive." (Guidelines, p.20)	Such a plasmid is not available (Curtiss et al., p.3). Furthermore, it is not definite that χ1776 has a suppressor mutation at all (see this paper, §§5a and 5b). A "safe" plasmid would depend, for its replication, on the existence of a suppressor mutation in the host. In addition, Stewart and Levin (in press) demonstrate that plasmids will establish themselves in a bacterial population even when their introduction into the host markedly reduces its Darwinian fitness.

Provisional NIH Guidelines:	χ1776 and χ1876.
"Conjugation minus mutations that reduce the ability of conjugative plasmids to enter the plasmid-host complex ... should reduce mobilization of the cloned DNA to other strains ..." (Guidelines, p.19)	The mentioned effects are not always obtained. With some of the plasmids tested, mobilization seems to be almost unimpaired when compared to the conjugation-plus parent (Curtiss et al., Appendix A, see this paper, §§15, 16, 17, 18, and 19).

IV. CRITIQUE OF "CONSTRUCTION, PROPERTIES AND TESTING OF χ1776"

We divide our criticism of the "Construction, Properties and Testing of χ1776" into two sets of comments-- those dealing with the experiments which have been reported and those suggesting some experiments which have yet to be done to satisfy the criteria required of an EK-2 host-vector system according to the NIH Proposed Guidelines for Research Involving Recombinant DNA Molecules (January 1976).

A. EXPERIMENTS REPORTED

Strain construction:

§1. The construction of χ1776 from χ1276 (W1455) involved the use of three major techniques for the introduction or removal of markers: conjugation, transduction by P1L4, and nitrous acid mutagenesis. During this construction isogenecity to the parent strain was not maintained, so that comparisons between the phenotypes of the two strains cannot be based only on the marker differences intentionally introduced.

§2. Several markers introduced into this strain are uncharacterized. This class includes:

a) the reverted thermosensitive lesion cotransduced into χ1678 with the *dapD8 tonA53* marker pair,

b) the nalidixic acid resistance allele,

c) the unexpected rfb-2 "allele"/phenotype obtained concommittant with the removal of the *his*-53 allele, and

d) the thermosensitive mutation unintentionally cotransduced with the presumed *thyA57* allele.

§3. The direct use of nitrous acid to induce anaerobic chlorate resistance in χ1846 to produce χ1849 may be unwise, since nitrous acid, a generalized mutagenic agent, may introduce additional uncharacterized

alleles into χ1849 which could be maintained throughout the remainder of the construction, and thus be present in χ1776.

§4. The introduction of the thyA57 allele by P1L4 transduction (which, it is important to note, carried with it an associated uncharacterized thermosensitive mutation, see §2d, above) was not controlled by monitoring the cotransduction of a linked marker. This could have been accomplished by simply cotransducing the closely linked marker pair thyA57-lysA32 (0.3 minutes apart).

Genotypic characterization:

§5. supE42:

a) The presence of the supE42 mutation was assayed by the ability of χ1776 thr$^+$ transductants to plate $\lambda cI_{857}N_7N_{213}$ at an efficiency of 10^{-3} Curtiss et al. conclude from this observation that either expression of the supressor has been modified or that the abilities of λvir (control) and $\lambda cI_{857}N_7N_{213}$ to productively infect χ1776 thr$^+$ derivatives differ. Curtiss and co-workers favor the latter hypothesis since $\lambda cI_{857}N_7N_{213}$ fails to plaque on glucose-grown cells. However, this phenomenon is well-characterized; lambda adsorbs, as a rule, poorly on glucose-grown cells, since its receptor, specified by the malB gene is subject to catabolite repression (Maxime Schwartz, personal communication). Controls for the relative adsorption efficiencies of λvir and $\lambda cI_{857}N_7N_{213}$ on maltose-grown versus glucose-grown cells are not presented.

b) Alternative explanations for the observed lowering of plating efficiencies of $\lambda cI_{857}N_7N_{213}$ include the possibility that an additional phenotype resembling nus (Friedman, 1971) or gro:

(Georgopoulos, 1971) has been introduced into χ1776, or since λN^- mutants are by nature leaky, there is no suppressor present and these results are due to leakiness. The proper assay for the presence of the supE42 allele would be to ask for suppression of an amber (e.g., $\lambda placZ_{am}$ in a lac^- background) whose gene expression can be assayed directly.

§6. The thyA57 allele was found to revert in χ1776, which does not occur in all other strains tested for reversion of thyA57. It is not clear whether the thyA57 allele is the marker present in χ1776 conveying the thy^- phenotype, since no control cotransduction marker was used in its introduction (see this paper, §4).

§7. The uncharacterized rfb-2 mutation (see this paper, §2c) reverts at a low frequency. However, since this allele confers a multiple phenotype on χ1776 (sensitivity to bile salts, detergents, antibiotics, and drugs; conjugation deficiency; and partial resistance to phage P1), Curtiss et al. (p.11) conclude that revertants of this allele "have numerous associated changes, that in some respects compromise the safety of χ1776 and χ1876."

Phenotypic characterization:

§8. DAP-less death:

a) DAP-less death for χ1776 proceeds more rapidly in conditions under which cells can carry out macromolecular synthesis than in more minimal starvation media (e.g., BSG, distilled water, tap water). This indicates that the strain is more likely to survive in poorer (natural "famine") environments than in richer (laboratory) environments.

b) DAP-less death curves for χ1876 indicate that a culture undergoing death contains two populations of cells, one of which dies

more slowly and is able to grow back five orders of magnitude after 100 hours of starvation in DAP-less media (Curtiss et al., Figure 10). The possibility that these survivors are in fact genotypic revertants to the phenotype of DAP-less death was not ruled out. In addition, it seems that the parents to χ1876, χ1846 and χ1849, die faster than χ1876 and lack the resistant population present in χ1876 cultures (Curtiss et al., Figure 11).

c) When DAP-less death of χ1876 is observed in the presence of the parent χ289, χ1876 initially dies and then stops dying by 4 to 9 hours "as though being crossfed or protected by χ289" (Curtiss et al., p.17, Figure 16). Curtiss et al. then conclude, on the basis of a single datum-point at a late time (24 hours), that χ1876 dies rapidly after 9 hours. These data are in seeming contradiction to findings presented later, which demonstrate that χ1876 can conjugate with recipients under similar conditions for much longer times than it is supposedly alive.

It is not at all clear whether χ1876 exhibits its DAP-less death phenotype when other cells are present to the extent claimed by Curtiss et al.

d) The "rfb-2" phenotype is completely masked by the DAP-less death phenotype, since the additional presence of bile salts or detergents when a culture is undergoing DAP-less death does not increase the death rate of the culture appreciably.

§9. Thymineless death:

a) Thymineless death is not complete, and prolonged starvation leads to regrowth of cells which are genotypically resistant (deoB, deoC) to thymineless death (curtiss et al., Figure 19).

b) It is also not clear whether rescue after thymineless death is due to regrowth of resistant cells or to the addition of thymine, since

the proper control (following the time course of death without thymine after 20 hours) was not included in the presentation.

c) Thymineless death does not occur at high cell densities and death at low densities appears to cease after 8 to 12 hours of starvation (Curtiss et al., Figure 20). This phenotype may not be expressed in environments where cell density is high, such as in human individuals who have a high concentration of bacteria in the gut, or as in densely populated raw sewage.

§10. Thymineless DAP-less death:

a) Thymineless death and DAP-less death phenotypes do not act cooperatively or synergistically in that the death rate under combined starvation conditions is similar to the rate of death during either DAP or thymine starvation conditions singly in all media tested excepting supplemented ML (Curtiss et al., Figure 19).

b) Although slow regrowth of cultures was not observed under this "test of fire", under the most minimal of conditions tested, greater than 1.0% of both χ1776 and χ1876 survived up to 36 hours of starvation (Curtiss et al., Figure 22).

c) In addition, whereas χ1776 died out almost completely by 216 hours (9 days), 0.1% of χ1876 survived for 9 days in the most minimal of nutrient starvation media tested (ML + Glc, Thr, Met, Bio, Lys). The addition of the suplemental piece of DNA (pSC101) into χ1776 enables the strain to survive much better under starvation conditions.

d) This evidence (§10c, immediately above) is the first direct evidence presented demonstrating that the addition of a supplemental piece of DNA into the χ1776 disarmed host improves the viability of that host

under a specified set of conditions that directly measure its ability to survive.

§11. DNA degradation during DAP-less and/or thymineless death:

a) Thymineless death does not result in degradation of the DNA of the cell, contrary to findings with other K12 strains (Onkawa, 1975). Perhaps this is due to the absence of a restriction-modification system, since DNA degradation is not observed during the thymineless death of the restrictionless, modificationless *E. coli* C (Baker and Hewitt, 1971).

b) DNA degradation during thymineless DAP-less death for both χ1776 and χ1876 is only at best 50% complete by 12 hours at all cell densities measured (Curtiss et al., Figure 24).

c) Minicells containing plasmid DNA from χ1876 are immune to thymineless death (Curtiss et al., p.18).

§12. Survival in non-growth media:

a) Both χ1776 and χ1876 survive as well as the parent strain χ289 in several minimal environments including tap water and deionized water, within the limits of experimental error for the measurements (Curtiss et al., Figures 25, 26, and 27). (The survival titers for the three strains were within a factor of 10 of an average of 5 logs of killing over a period of 8 days for a specific medium).

b) χ1776 and χ1876 demonstrate no loss of viability over a period of two weeks at 4^{o}C when stored in growth medium or one of the starvation media (BSG) (Curtiss et al., p.19).

§13. Survival during drying:

To within experimental error, there is no difference in survival of χ289, χ1776, and χ1876 during the effects of drying at room temperature

(Curtiss et al., Figure 28).

§14. Survival during passage through rats:

a) The design of the feeding experiment, in particular, the sample sizes of the rats used to test a particular bacterial strain (3, 6, and 9 rats strain^{-1}) does not allow for fluctuations from a normal distribution in the variety of responses of rats to *E. coli*. *E. coli* is known to have widely different passage properties through individual humans, and there is no evidence to the contrary of the existence of a wide range of passage responses to *E. coli* in younger rats (to our knowledge, there is no set of experiments reported that speak directly to this point). Furthermore, there are no indications that the rat gut environment is similar enough to the human gut environment with respect to response of the gut to *E. coli* to allow for a direct comparison. Although we question the statistical significance of these results a priori with respect to design, we offer two additional criticisms to assist in the design of similar experiments in the future.

b) Examining the results, Curtiss et al. conclude, "It is therefore evident that the six hours it takes a fed strain to appear in feces is an insufficient length of time to permit enough growth for 100% DAP-less death to occur. In reality, we do not even know whether DAP is or is not present in the intestinal contents to spare dap$^-$ strains from DAP-less death, although the reduced survival of DAP$^-$ strains can be used to argue that free DAP is probably not plentiful in the intestine." (Curtiss et al., p.19) This is circular reasoning; it foregoes the conclusion that the death of the cell in the GI tract is due primarily to the DAP-less death phenotype.

c) In addition , " The feeding of tetracycline to rats for one day prior to and during feeding of χ1876 results in survival of some χ1876 cells." (Curtiss et al., p.21) This is astonishing, for it seems that the presence of the pSC101 plasmid, by virtue of its tetracycline-resistance marker, enables χ1776 (χ1876) to survive passage through the rat gut in the presence of tetracycline. Furthermore, this phenotype overrides all of the mutational barriers (dapD8, thyA57, Δ40, rfb-2) intentionally established to prevent survival. These data are even more surprising in that they do not consider the inactivation of tetracycline in vivo by the milk in which the strains were administered. In addition, a bile salts resistant derivative of χ1876 (which occurred upon spontaneous reversion of χ1876, see this paper, §7) gives higher survival titers under the same conditions.

Potential for Transmissability of Genetic Information by Strains:

§15. Conjugational recipient ability under permissive conditions:

Of the 14 plasmid incompatability groups examined, 9 are reduced less than 100 fold and 6 are reduced less than 20 fold in their proficiency to serve as donors to χ1776 at at least one of the two temperatures, 32°C and 37°C (Curtiss et al., Table 18, Appendix A).

§16. Mobilization of pSC101 by conjugative plasmids under permissive conditions:

χ1876 exhibits the same donor ability as the parent χ1753 under permissive conditions for 5 out of the 7 plasmids tested (Curtiss et al., p.24, Appendix A). Moreover, since phenotypic expression of the tetracycline marker on the pSC101 plasmid was not allowed for in the

design of these experiments, the proficiencies of donor-ability are underestimates.

§17. Triparental matings under permissive conditions:

a) In triparental matings using χ1753 as primary donor of 9 different plasmids, χ1876 as primary recipient and secondary donor, and χ1763 as secondary recipient to measure the R-mediated transfer of pSC101 to χ1763 [χ1753(R)→χ1876(pSC101)→χ1763, pSC101 scored by *tet*^{r}], only one plasmid failed to produce transconjugants. Additionally, some of the R-factors in the experiment which yielded transconjugants did not yield transconjugants with χ1876 as primary (R) donor [χ1876(R)(pSC101)→χ1763, pSC101 scored by *tet*^{r}] (Curtiss *et al.*, Tables 21 and 22). This suggests that χ1876 may be a more proficient donor upon recent receipt of the R-factor than when it originally harbors the R-factor. Alternatively, pSC may be mobilized more efficiently upon receipt of the R-factor by some unknown catalytic mechanism.

b) Although the frequency of R549*drd1* transfer from χ1783 to χ1876 is 10^{-4} of that from χ1783 to χ1763, the frequency of pSC101 mobilization mediated by R549*drd1* from χ1783 to χ1876 to χ1763 is 100 to 1000 times more frequent than the frequency from χ1783 to χ1876 [χ1783(R549*drd1*)→χ1876(pSC101)→χ1763, pSC101 scored by *tet*^{r} >> χ1783(R549*drd1*)→χ1876(pSC101), R549*drd1* scored] (Curtiss *et al.*, p.25, Tables 18 and 22). These data are incrongruous, if not contradictory. They emphasize the point that the proficiencies of donor-ability for χ1876 are underestimates (see this paper, §16 above) in the sense that χ1876 is a more proficient recipient for R549*drd1* than previously measured.

§18. Conjugational ability during DAP-less and/or thymineless death:

Transfer of R1drd19 by χ1776 to χ1763 occurs during starvation at a rate proportional to the donor cell death rate (Curtiss et al., p.25). Donor ability is not impaired by starvation conditions to an extent greater than viability.

§19. Conjugational ability as a function of starvation time in non growth liquid media:

Donor ability is exhibited at 37°C after starvation of R1drd19^{+}-containing χ1776 for 24 hours in BSG (Curtiss et al., p.26).

§20. Potential for transductional transmission under non-permissive conditions:

a) Both χ1776 and χ1870 can support growth of bacteriophage T6 under nonpermissive conditions (Curtiss et al., Figures 29 and 30).

b) χ1776 is sensitive to 434, a specialized transducing phage, and partially sensitive to P1, a generalized transducing phage. It is probably sensitive to many uncharacterized and unknown specialized and generalized transducing phages. It is sensitive to BF23, which can recombine with T5, which in turn shares part of its host range with generalized transducer T1, the three phages are morphologically similar, etc.)

§21. Potential for transformation under nonpermissive conditions:

Although χ1776 DNA is rapidly degraded by an intestinal extract of rats, it is not clear whether or not this situation is duplicated in vivo, and the experiment presented does not test this hypothesis (Curtiss et al., p.27).

B. SOME EXPERIMENTS WHICH HAVE YET TO BE PERFORMED

§22. The testing of a modified *Escherichia coli* EK-2 host-vector system must assess its viability in other than specifically designed and carefully regulated laboratory environments. These environments should represent, most reasonably, naturally occurring environments which *E. coli* is known to inhabit. These environments include soils, raw sewage, arthropod intestinal tracts, and the human gut. Since there is a wide range of passage response to *Escherichia coli* among the human population, any EK-2 host should be tested for survival in the human GI tract prior to certification. In addition, given the data presented on the survival of χ1776 and χ1876 in tap water, the likelihood of χ1776 reaching the sewer were it accidentally poured down a drain, is quite high. Raw sewage is a rich environment harboring a plethora of possibilities for genetic exchange between coliform and other types of bacteria, as evidenced by the diversity and number of coliphages one finds in a small volume of raw sewage (R. Goldstein, unpublished results).

§23. The genetic construction of an EK-2 strain from a parent strain should be done as isogenically as possible, so that comparisons of phenotype do not rely on markers other than those intentionally introduced. The presence of secondary metabolic systems such as ebg (Campbell, Lengyel, and Langridge, 1973) which can rescue function of a particular allele by bypassing the normal biochemical pathways employed by *E. coli* in the laboratory, in other than a laboratory environment, should be assessed directly by testing in a number of different natural environments.

§24. If a strain as complex as χ1776 (in the sense of having many mutational markers) were distributed among many laboratories wishing to

engage in recombinant DNA research using this strain as host, how fast would that strain evolve in the laboratory? Were the strain sampled at regular intervals after dispensation, how soon would ther arise genotypic or phenotypic differences from the parent? It is important to point out that markers are frequently lost during the normal handling of a complex auxotroph, and that some markers are so detrimental to a cells growth that they are routinely lost during continuous handling (e.g., glnE, Greg Pahel, personal communication). How dispensation and use of any EK-2 candidate system will alter the genotypic and/or phenotypic properties of the system should be assessed prior to certification.

§25. The strain χ1876 produces large numbers of pSC101-containing minicells which are capable of surviving under conditions of thymineless death. The capacity of these minicells to act as genetic donors in triparental matings should be discerned. Can the minicells "survive" to disseminate plasmid-carried information under conditions under which the host cells cannot (see this paper, §11c)?

§26. The possibilities that the DAP-less and thymineless death phenotypes could be rescued by in vitro crossfeeding (see this paper, §§8 and 9c) are neither ruled out completely nor examined extensively.

§27. The introduction of drug-resistance markers to facilitate monitoring may confer additional survival phenotypes upon the host strains in environments not considered in the testing of χ1776.

§28. The possibilities that χ1776/χ1876 DNA could transform bacteria other than *E. coli* in the gut was not examined. There may exist in the normal bacterial flora of the human gut cells capable of recieving

transforming DNA from starved or dying cells at a high frequency.

§29. Transformational ability as mediated by a lambdoid helper has not been assessed for χ1776 or χ1876. This could be performed by looking at λh^{434}-mediated transformation under a diverse set of environmental conditions.

V. REFERENCES

1) Curtiss et al., "Construction, Properties and Testing of χ1776", submitted to the NIH Recombinant DNA Molecule Program Advisory Committee, March 30, 1976.

2) Boston Area Recombinant DNA Group, "Critique of NIH Guidelines", submitted to the NIH Recombinant DNA Molecule Program Advisory Committee, December 1975.

3) Baker and Hewitt, J. Bact. 105: 733, 1971.

4) Campbell, Lengyel, and Langridge, Proc. Natl. Acad. Sci. US 70: 1841, 1970.

5) Friedman, in "The Bacteriophage Lambda", ed. A.D. Hershey, p.733, 1971.

6) Georgopoulos, in "The Bacteriophage Lambda", ed. A.D. Hershey, p.639, 1971.

7) Frazer and Curtiss, in "Current Topics in Microbiology and Immunology" 69: 1, 1975.

8) Stewart and Levin, Genetics, in press, 1976.

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. an infant	:	
Plaintiff	:	Civil Action No. 77-0916
v	:	
JOSEPH A. CALIFANO, JR. et al	:	FILED
Defendants	:	FEB - 6 1978

JAMES F. DAVEY, Clerk

SUPPLEMENTAL AFFIDAVIT OF CHRISTINE OLIVER IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION

I Christine Oliver being first duly sworn state as follows:

I have read and am familiar with the document entitled IMUA-18, and the statement of understanding and agreement dated May 23, 1977. The opinions expressed by me in my previous affidavit filed in this case are unchanged. At the time those opinions were expressed, I was familiar with the E. coli which this document indicates will be utilized for the Ft. Detrick experiments.

Christine Oliver
Christine Oliver

STATE OF ~~MASSACHUSETTS~~ New York)
) ss:
COUNTY OF Ny)

I HEREBY CERTIFY that before me, a Notary Public, in and for the State and County aforesaid, personally appeared Christine Oliver and acknowledged the foregoing Supplemental Affidavit to be her voluntary act and deed.

WITNESS my hand and notarial seal this 23 day of Jan, 1978.

Theresa M Torsewick
Notary Public

My Commission expires

THERESA M. TORSEWICK
Notary Public, State of New York
No. 41-4600739
Qualified in Queens County
Commission Expires March 30, 1978

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE MARYLAND
20850

301 279-2230

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. an infant	:	
Plaintiff	:	Civil Action No. 77-0916
v	:	
JOSEPH A. CALIFANO, JR. et al	:	
Defendants	:	

FILED

FEB - 6 1978

JAMES F. DAVEY, Clerk

SUPPLEMENTAL AFFIDAVIT OF STEPHEN HAVAS IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION

I Stephen Havas being first duly sworn state as follows:

I have read and am familiar with the document entitled IMUA-18, and the statement of understanding and agreement dated May 23, 1977. The opinions expressed by me in my previous affidavit filed in this case are unchanged. At the time those opinions were expressed, I was familiar with the E. coli which this document indicates will be utilized for the Ft. Detrick experiments.

Stephen Havas

STATE OF ~~MASSACHUSETTS~~ New York)
) ss:
COUNTY OF New York)

I HEREBY CERTIFY that before me, a Notary Public, in and for the State and County aforesaid, personally appeared Stephen Havas and acknowledged the foregoing Supplemental Affidavit to be his voluntary act and deed.

WITNESS my hand and notarial seal this 23 day of Jan, 1978.

Theresa M. Torswick
Notary Public

My Commission expires

THERESA M. TORSWICK
Notary Public, State of New York
No. 41-4633709
Qualified in Queens County
Commission Expires March 30, 1978

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE MARYLAND
20850
301 279-2230

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. an infant	:	
Plaintiff	:	Civil Action No. 77-0916
v	:	
JOSEPH A. CALIFANO, JR. et al	:	
Defendants	:	

FILED

FEB - 6 1978

JAMES F. DAVEY, Clerk

SUPPLEMENTAL AFFIDAVIT OF STUART NEWMAN IN SUPPORT OF MOTION FOR A PRELIMINARY INJUNCTION

Stuart Newman, being first duly sworn, states as follows:

I have read and am familiar with the document entitled IMUA-18, and the Statement of Understanding and Agreement dated May 23, 1977. The opinions expressed by me in my previous affidavit in this case are unchanged. My criticism of the experiment remains that if the organisms involved in the experiment escape into the environment there would be no barrier between the organisms and the persons living in the populated area where the experiments are to take place.

Stuart Newman
Stuart Newman

STATE OF NEW YORK)
) ss
COUNTY OF Albany)

I hereby certify that before me, a notary public in and for the State and County aforesaid, personally appeared Stuart Newman who acknowledged the foregoing Supplemental Affidavit to be his voluntary act and deed.

WITNESS my hand and notarial seal this 31st day of January, 1978.

Sharyn Desroches
Notary Public

SHARYN DESROCHES
Notary Public, State of New York
Qualified in Albany County
My Commission Expires March 30, 19 79

My Commission expires 3-30-79

FERDINAND J. MACK
ATTORNEY AT LAW
SUITE 106
OLD TOWN CENTER
17 WEST JEFFERSON ST.
ROCKVILLE, MARYLAND
20850

301 279-2230

UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR. Plaintiff	)	
v.	)	Civil Action No. 77-0916
JOSEPH A. CALIFANO, JR. SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, et al. Defendants	)	

AFFIDAVIT

I. Bernard Talbot, M.D., Ph.D., being duly sworn, depose and say:

1. I am the Special Assistant for Intramural Affairs, National Institutes of Health, Department of Health, Education, and Welfare, and have held this position since June 1975.

2. The document IMUA-18, which describes the proposed experiments which plaintiff seeks to enjoin, says that EK2 host-vector systems will be used in these experiments. EK2 host-vector systems are super-safe derivatives of E. coli K-12.

3. The first two EK2 host-plasmid systems certified by NIH were χ1776 (pSC101) and χ1776 (pCR1); these were certified by the Director, NIH, as EK2 host-vector systems on December 6, 1976.

4. Recently submitted by the plaintiff to the court in this case is a Supplemental Affidavit of Ruth Hubbard In Support of Motion For Preliminary Injunction, dated January 25, 1978. Attached to this is a document, entitled "Analysis and Critique of the Curtiss Report on the Escherichia Coli Strain Intended for Biological Containment in DNA Implantation Research," by Richard Goldstein, Christian Orrego, and Philip Youderian, Boston Area Recombinant DNA Group, submitted to the NIH Recombinant DNA Molecule Program Advisory Committee, May 30, 1976 (hereinafter called the "Boston Area Recombinant DNA Group Critique").

5. The Boston Area Recombinant DNA Group Critique was carefully considered by NIH before χ1776 (pSC101) and χ1776 (pCR1) were certified by NIH as EK2 host-vector systems.

6. On December 2, 1976, I wrote a memorandum to Dr. Donald S. Fredrickson, Director, NIH, on the subject "EK2 Certification of χ1776

(pSC101) and χ1776 (pCR1)." Appended to this memorandum were hundreds of pages of documentation, arranged under Tabs A through L. A copy of this December 2, 1976, memorandum with all attachments (except that, for the sake of brevity, the 147-page submission appearing under Tab E has been omitted) is appended to this affidavit (this will hereinafter be called the December 2, 1976, memorandum).

7. Under Tab B of the December 2, 1976, memorandum is a copy of the Boston Area Recombinant DNA Group Critique.

8. Under Tab A of the December 2, 1976, memorandum is a detailed letter to Dr. Fredrickson, Director, NIH, from Dr. Edward Adelberg, Professor of Human Genetics, School of Medicine, Yale University, and Chairman of the Working Group on Safer Hosts and Vectors responding point-by-point to the Boston Area Recombinant DNA Group Critique.

9. Under Tab C of the December 2, 1976, memorandum appears a memorandum describing my telephone calls to the four other members of Group 1 (Host-plasmids) of the Working Group on Safer Hosts and Vectors. They all agreed with Dr. Adelberg's response to the Boston Area Recombinant DNA Group Critique.

10. Tab D of the December 2, 1976, memorandum contains a history of the detailed and extremely careful steps taken toward the certification of χ1776 (pSC101) and χ1776 (pCR1) as EK2 host-vector systems. Tabs E through K contain voluminous documentation referred to under Tab D.

11. Tab L contains the memorandum signed by Dr. Fredrickson on December 6, 1976, certifying χ1776 (pSC101) and χ1776 (pCR1) as EK2 host-vector systems.

Bernard Talbot

Bernard Talbot, M.D., Ph.D.
Special Assistant for Intramural Affairs
National Institutes of Health

SUBSCRIBED AND SWORN TO BEFORE ME

THIS 7th DAY OF February 1978

Esther G. Abelow
Notary Public

My commission expires My commission expires July 1, 1978.

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, Jr., an infant, Plaintiff,	)	
v.	)	Civil Action No. 77-916
JOSEPH A. CALIFANO, Jr., et al., Defendants.	)	

DEFENDANTS' RESPONSE TO PLAINTIFF'S SUPPLEMENTAL MEMORANDUM

Plaintiff has submitted supplemental affidavits from four of its five previous affiants which merely indicate that their previous affidavits still stand. But, as previously indicated, all that those prior affidavits establish at best is a purely speculative possibility that the stringent and excessively conservative physical and biological containment requirements of the NIH Guidelines will somehow prove ineffective. Plaintiff's supplemental memorandum in support of its motion for a preliminary injunction similarly adds nothing new. As shown in our previous memorandum in opposition to plaintiff's motion for a preliminary injunction and further demonstrated below, plaintiff's arguments and affidavits are legally and factually insufficient to justify a preliminary injunction.

None of plaintiff's affidavits establishes that the purported harm from the experiment is at all likely to actually occur. This is not surprising given the extraordinary measures employed by the NIH Guidelines to insure that no harm flows from the experiment. And the Nutter Affidavit shows that the experiment at issue here poses no added risks to humans or to the environment. Plaintiff's attempt to show that the experiment here is somehow special and requires further NEPA analysis is unsupported by the record. Rather, the record shows that NIH has carefully considered the potential risks of this experiment and all experiments conducted under the Guidelines to assure no risk of harm to human health or to the environment.

Significantly, mere speculation such as that contained in plaintiff's affidavits is legally insufficient to support the extraordinary remedy of preliminary injunctive relief. The heavy burden of proof required has recently been summarized as follows:

> Injunctive relief is appropriate only "to prevent existing or presently threatened injuries" and "will not be granted against something merely feared as liable to occur at some indefinite time in the future." Connecticut v. Massachusetts, 282 U.S. 660, 674 (1930). See also, General Fireproofing Company v. Wyman, 444 F.2d 391, 393 (2d Cir. 1971). Injunctions will not be granted where the injuries complained of are prospective and "which may, indeed, never occur." Crimmins v. American Stock Exchange, Inc., 346 F.Supp. 1256, 1262 (S.D. N.Y. 1972). The injury complained of must be of such imminence that there is a "clear and present" need for equitable relief to prevent irreparable harm. Hershey Creamery Co. v. Hershey Chocolate Corp., 269 F.Supp. 45 (S.D.N.Y. 1967); see also Assn. of Professional Engineering Personnel v. Radio Corp. of America, 183 F.Supp. 834 (D.C.N.J. 1960).

Ashland Oil, Inc. v. F.T.C., 409 F.Supp. 297, 307 (D. D.C. 1976) (emphasis in original). See also, Chacon v. Granata, 515 F.2d. 922, 925 (5th Cir. 1975), cert. denied, 423 U.S. 930 (1976) ("injunction is appropriate only if the anticipated injury is imminent and irreparable").

Thus, it takes more than speculation to support preliminary injunctive relief. In Capobianco v. First National Bank, 372 F.Supp. 416, 420 (M.D. Pa. 1974), Judge Muir held that the fear of possible adverse business decisions to be made in the future "is too speculative for judicial intervention on a preliminary injunction." As the court recognized, "fear

of harm lurking only theoretically in the future does not justify the drastic imposition of a preliminary injunction. [Citation omitted]." 372 F.Supp. at 420.

Although plaintiff's alleged harms speculated to flow from recombinant DNA research are admittedly different than the kinds of harm involved in the above cases, the legal principle is the same. Weighed against plaintiff's mere speculation that the rigid physical and biological containment features of the NIH Guidelines might somehow fail is the considered judgment of the experts at NIH and of the vast majority of the scientific community that the experiment poses no risk whatsoever. In sum, plaintiff's evidence shows no factors not fully considered in the NIH Guidelines and environmental impact statement.

Thus, plaintiff's affidavits are not based on any real evidence in the record and are entitled to little weight. In a different context the court of appeals has recently recognized that speculation is not enough to support a cause of action. The court recently affirmed Judge Platt's decision that "opinion based solely on speculation and hypotheses and [that] is unsubstantiated by any evidence in the record. " should be accorded little weight and cannot block a summary judgment. Merit Motors, Inc. v. Chrysler Corp., 417 F.Supp. 263, 272 (D. D.C. 1976), aff'd, ____ F.2d ___, _____ U.S.App.D.C. _____ (No. 76-1917, December 20, 1977), sl. op. at 12. Plaintiff's affidavits here are similarly speculative and are insufficient to support a preliminary injunction.

Moreover, plaintiff has offered no factual arguments concerning the experiment not already carefully considered by NIH. Although plaintiff has put one additional document before the Court in an attempt to bolster its exceedingly weak showing of potential harm, that report was already considered in detail by NIH before the experiment. Attached to the Supplemental Affidavit of Ruth Hubbard, dated January 25, 1978, is a May 30, 1976, memorandum discussing the appropriateness of using enfeebled strains of E. coli in recombinant DNA research. But, as the Affidavit of Dr. Talbot demonstrates, this report was analyzed in detail by NIH prior to approval of the E. coli strain discussed in the document. Attached as an exhibit to the Talbot Affidavit is the administrative record on approval of the EK2 system which shows that plaintiff's concerns were considered carefully by NIH and by independent expert advisors prior to approval. Thus, this report was thoroughly evaluated by NIH prior to approval of the research at issue here.

Accordingly, because plaintiff has failed to offer substantial new support for its motion for a preliminary injunction, the motion should be denied for the reasons explained in our prior opposition to plaintiff's motion.

Respectfully submitted,

L. MARK WINE
Land and Natural Resources Division
Department of Justice
Washington, D. C. 20530
(202) 739-2712

GARY B. RANDALL
Land and Natural Resources Division
Department of Justice
Washington, D.C. 20530
(202) 739-3796

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that I have served copies of the foregoing Defendants' Response to Plaintiff's Supplemental Memorandum and Affidavit, upon the below-listed addresses on this 10th day of February, 1978:

Ferdinand Mack, Esquire
17 West Jefferson Street
Rockville, Maryland 20850

William I. Althen, Esquire
Kilcullen, Smith and Heenan
1800 M Street, N. W.
Washington, D. C. 20036

L. MARK WINE

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

FERDINAND J. MACK, JR., an infant,

Plaintiff

v. Civil Action No. 77-916

JOSEPH A. CALIFANO, JR., ET AL.,

Defendants

AFFIDAVIT IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER

1. I, Stuart Newman, Ph.D., am an Assistant Professor of Biological Sciences at the State University of New York at Albany, and have held this position for the past two years.

2. I have read and am familiar with a document entitled Proposed Experiments on the Biological Properties of Polyoma Recombinant DNA Cloned in Bacteria Cells, by M.A. Martin and W.P. Rowe (the "Protocol"), for the conduct of experiments in Building 550 at Ft. Detrick, Maryland.

3. It is proposed by the investigators to manufacture novel organisms in which bacteria (E-coli) closely related to a strain known to colonize the human digestive, urinary, and respiratory tracts will carry and reproduce the genetic information of a virus (polyoma) known to cause cancer in certain species of mammal. These bacteria and their resident plasmids or bacteriophages containing the cancer virus genes will then be introduced by various routes into mice and mouse tissue culture cells. Finally, evidence of productive virus infection in the animals or cells will be assayed.

Rec'd 1/12/78

DEFENDANT'S EXHIBIT NO. 1

4. I see several serious hazards associated with the protocol. First, while handling of the recombinant organisms containing polyoma genes is planned to take place under P-4 (highest containment) conditions such facilities are not foolproof: Fort Detrick has had at least one reported mishap under P-4-like conditions in the past. In the case known to me an infectious agent escaped containment as a result of a syringe puncturing a worker's hand through a glove-box glove. Thus, though the chances are minimized, escape from physical containment is possible. The probability increases drastically under the P-2 conditions in which the investigators want to perform their immunologic assays. The switch to minimal containment will depend on demonstrating that heat-treated serum is free of E-coli or bacteriophage lambda. Such a determination is subject to human error and technical failure.

5. Were a recombinant organism to escape physical containment its likelihood of survival will depend on a variety of factors. The E-coli strain to be used (K-12) is not an inhabitant of the normal human intestine, but does survive in germ-free intestines of laboratory animals. More to the point, strains of E-coli can infect the blood and colonize the pharyax. The degree to which K-12 can do this has not been studied. Considering the more likely of the possible routes of escape under P-4, P-3, and P-2 conditions, this is a grave omission.

6. Once released into the environment recombinant organisms are self-reproducing and cannot be recalled. Even the most debilitated E-coli developed to date can survive for up to eight days in tap water. On lysing,

any bacterium can transfer genetic information to a more robust host. Since bacteria are ubiquitous, the polyoma genes could eventually be disseminated throughout the ecosystem. At present they are limited in their range by the adaptedness of their normal packaging to certain species of mammal.

7. Could polyoma genes harm man or any other organism outside their normal host range? At present virtually nothing is known about the mechanisms by which polyoma and other viruses cause cancer. Most cell biologists suspect that the basic mechanisms are not numerous. Different susceptibilities to a given virus among different species of mammal could represent aspects of recognition that have little to do with the underlying basis of transformation to the cancerous state. When cancer causing genes are reproduced apart from their normal packaging (which after all, is what is recognized by the exposed organism) in hosts which can survive in a wide variety of higher organisms, including man, their carcinogenic effectiveness could be enhanced in those organisms.

8. No details are given on the proposed handling of the "inactivated bacterial lysates". But as the genetic information in this material can be taken up by a wide variety of bacteria, the transfer of this material between laboratories presents a unique hazard to the ecological system.

Stuart A. Newman

Kathleen M. Pickett
KATHLEEN M. PICKETT
Notary Public, State of New York
Qualified In Saratoga
My Commission Expires March 30, 1979

5/16/77

Doc # 4607842

I. IDENTIFICATION

A. Laboratory Chiefs: Wallace P. Rowe, M.D., Chief, LVD/NIAID

Norman P. Salzman, Ph.D., Chief, LBV/NIAID

B. Investigators: Dr. Wallace P. Rowe

Dr. Malcolm Martin

1. Laboratory/Branch/BID:

Laboratory of Biology of Viruses; and Laboratory of Viral Diseases, NIAID

*2. Buildings:

Mobile Containment Laboratory located adjacent to Bldg. 21 (NIH)
Building 550, Frederick Cancer Research Center (Frederick, Maryland)
Building 5, Rooms 218 and 220 (NIH)

3. Telephone Numbers:

MCL (NIH)	496-5440
FCRC, Frederick	(301)663-7167
LVD/NIAID (NIH)	496-2613
LBV/NIAID (NIH)	496-4012

C. Other Individuals Who Will Participate In This Research:

Dr. Hardy Chan

Dr. Mark Israel

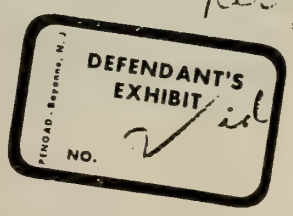
Dr. Aurobindo Roy

Mr. Raleigh Boaze

D. Risk Classification:

1. For Group I Agents (recombinant DNA molecule research): with E. coli K12 containment systems; P2, P3 and P4 and EK2.

*Where Research Is To Be Performed



II. EXPERIMENTAL RATIONALE

During the past two years, considerable interest has developed regarding the potential benefits and biohazards associated with the production of recombinant DNA molecules and their subsequent amplification in both prokaryotic and eukaryotic cells.

Many individuals have felt that an experiment involving the cloning of polyoma virus DNA in Escherichia coli, using either a lambdaphage or plasmid vector, and the subsequent inoculation of mice with the resultant organisms would be highly informative. We have been charged by the NIH Recombinant DNA Molecule Program Advisory Committee to plan and carry out such experiments utilizing facilities of suitable containment.

The reasons for selecting polyoma virus for such an experiment are manifold. Polyoma virus DNA is small (3×10^6 daltons), is well characterized chemically and physically, and is infectious in mice. The virus does not appear to replicate in human cells (Eddy, B. E., Virol. Monogr., 7: 114, 1969; Pollack, R. E. et al., J. Cell Physiol., 77: 117, 1971) presumably because it fails to adsorb or be uncoated. Microinjection of polyoma virions or supercoiled DNA into the cytoplasm of human cells in culture results in the synthesis of viral specific T antigen; no viral capsid (V) antigen or infectious virus was detected following such manipulation (Gruen et al., Virology 58: 290, 1974). However, the chief reason for its selection is the well-documented observation that parenteral inoculation of mice with minute doses of virus reproducibly leads to an immune response (Rowe et al., Journal of Experimental Medicine 109: 379, 1959; Rowe et al., Perspectives in Virology 2: 177, 1961). Feeding and intranasal instillation of virus are much less efficient modes of infection. This phenomenon is the basis for the mouse antibody production (MAP) test for polyoma virus. In this assay, mice from a polyoma-free colony are injected with test material and, three to four weeks later, are tested for serum hemagglutination inhibiting (HI) antibody against the virus. This test can detect approximately one tissue culture infectious dose (TCID) of polyoma virus: adults are as sensitive as suckling mice. We thus view the HI antibody to be a highly sensitive, unambiguous and convenient test reflecting the occurrence of a productive polyoma infection in mice. It is especially appealing in the context of the proposed studies which involve the use of an E. coli cloning system because it is a continuing test (i.e., a single group of mice, colonized by an E. coli plasmid or phage system containing a polyoma component, can be tested repeatedly for whether productive virus infection occurs during a prolonged period of observation). A second assay that will be employed to evaluate the oncogenic potential of bacteria containing a polyoma-DNA recombinant involves the intraperitoneal inoculation of test materials into newborn hamsters. In this assay (Stoker, British Journal of Cancer, 14: 679, 1960) polyoma virus-induced tumors involving the kidneys, heart, peritoneum, liver and lungs appear 2 to 4 weeks following injection; the number of foci of tumor cells in the kidneys can be roughly correlated with the initial virus dose. In this test system only a portion of the viral genome must function (viz. the "early" gene sequences containing the genetic information for "oncogenicity") for a positive result. This assay may prove most useful in this risk-evaluation study, particularly

in those cases where alterations have occurred in "late" polyoma genes. In such a situation, the MAP test would yield negative results, but the potential oncogenic activity of a polyoma containing DNA recombinant could still be unmasked if tumors develop in the hamsters.

In the following paragraphs we outline a series of experiments which will utilize polyoma virus in an attempt to answer some of the questions which have been raised about potential biohazards of recombinant DNA research. Specifically, we intend to generate recombinant molecules consisting of either polyoma virus and bacteriophage lambda DNAs or polyoma virus and plasmid DNAs, and clone such molecules in a suitable E. coli host. Progeny phage, or plasmid-containing E. coli will be fed to, and inoculated into mice and newborn hamsters in the final step of the proposed experiments and the animals tested for evidence of virus infection or tumor formation.

Although, at first sight, this seems to be a simple, straight-forward experiment which could be done cheaply and expeditiously, this is not the case. In particular, since we are very concerned that a negative result will be misinterpreted as indicating that there is little biohazard in DNA recombinant work, we feel that a number of variables must be evaluated, and that the experiments should be designed to maximize the chances of a positive result. Also, if negative results are obtained with a given system, we feel that the experiments should be continued with modified systems until we are reasonably convinced that a positive result is just not going to occur. Accordingly, our experimental strategy will be to conduct the cloning of polyoma DNA in E. coli in several different stages.

Our initial experiments will be conducted in strict accordance with the NIH Guidelines for Recombinant DNA Research. We will employ approved EK2 host-vector systems and P4 physical containment to clone polyoma DNA in E. coli. Mice and hamsters will be inoculated with bacteria containing polyoma DNA recombinants by a variety of routes as well as with the purified recombinant DNA; these animals will be maintained in P4 containment.

In addition to its importance for studying transfer of DNA from E. coli to host cells, we feel that the polyoma-E. coli system may be particularly useful for examining the question of expression of eukaryotic DNA in a bacterial cell. Accordingly, we will use appropriate nucleic acid hybridization, radioimmunoassay and other serologic procedures in an attempt to detect and quantitate synthesis of polyoma RNA, polypeptides and proteins.

III. DESCRIPTION OF THE AGENTS

A. Polyoma Virus

1. Strain "H", obtained from Dr. Thomas Benjamin, Harvard University (large plaque variant), Cambridge, Massachusetts

2. Toronto strain (McCulloch et al., Nature 183: 1535, 1959)

B. EK2 Lambda Vector System

1. Certified EK2 bacteriophage: λgt·λB (Tiemeier, T. et al., Nature 263: 526, 1976 and Leder, P. et al., Science 196: 175, 1977)

2. Host bacterium: E. coli Ymel, LE392

C. EK2 Plasmid Vector System

1. Plasmids: pSC101 and pCR1.

2. Host bacterium: E. coli χ1776 derived and obtained from Dr. Roy Curtiss, University of Alabama, Birmingham, Alabama, and certified EK2 by Director, NIH.

IV. DESCRIPTION OF THE TYPE OF EXPERIMENT

A. Eco RI cleaved polyoma DNA will be joined to the two largest Eco RI fragments of λgt·λB DNA using T4 DNA ligase. Polyoma-lambda (P-lambda) DNA recombinant molecules thus generated will be used to transfect E. coli. Infected E. coli, purified phage, or phage DNA will be inoculated into mice (adult, newborn, germfree, conventional) by oral, nasal, rectal, and parenteral routes after it has been demonstrated that P-lambda recombinant DNA is present in the infected cultures. In all cases the mice will be tested for the development of polyoma HI antibody, and in some cases, tumor formation. The animals will also be examined for changes in the virulence of E. coli such as sudden, unexpected death or diarrheal disease. Newborn hamsters will also be inoculated intraperitoneally with infected E. coli, phage, and purified P-lambda DNA and monitored for polyoma induced tumors. Mouse and rat cell tissue cultures will be infected with purified P-lambda DNA and monitored for the appearance of progeny virus, viral antigens, and transformed colonies.

B. Eco RI cleaved polyoma DNA will be ligated to Eco RI digested pSC101 or pCR1 DNAs and used to transform E. coli strain χ1776, a certified EK2 system. Clones transformed to antibiotic resistance will be screened by filter hybridization for the presence of polyoma-plasmid (P-plasmid) DNA. Bacteria containing P-plasmid DNA as well as purified P-plasmid DNA will be inoculated into mice, hamsters, and tissue cultures as described above.

C. Lysates of bacteria containing P-lambda or P-plasmid recombinant DNAs will be assayed for the presence of infectious polyoma virus using primary and continuous lines of mouse cells.

D. Bacterial lysates with no demonstrable biological activity will be examined for the presence of polyoma-specific RNA and proteins.

V. ASSESSMENT OF THE RISK

The experiments described in Section IV fall into at least two different categories (cloning of animal viral DNA in an E. coli host-vector system and the use of a polyoma vector system in mouse cells) of risk as outlined in the NIH Guidelines for Recombinant DNA Research.

The Guidelines state that P4 + EK2 or P3 + EK3 must be used to isolate DNA recombinants that include all or part of an animal virus genome. Since certified EK3 vectors are not presently available, the experiments we have outlined will be conducted under P4 containment with approved EK2 host-vector systems. These conditions can be met with the P4 Mobile Containment Laboratory, NIH, and Building 550, FCRC, and the two approved EK2 host-vector systems outlined in Section III. Because of the scope and complexities of the studies we plan to carry out, we have compiled a list of various activities and laboratory manipulations and grouped them according to the level of physical containment under which each will be conducted.

A. P4 Physical Containment

1. Propagation of P-lambda DNA Recombinants

   a. Transfection of E. coli with P-lambda DNA

   b. Identification of plaques which contain P-lambda DNA recombinants by colony hybridization

   c. Preparation and purification of P-lambda phage stocks

   d. Preparation of P-lambda infected E. coli

2. Propagation of P-plasmid DNA Recombinants

   a. Transformation of E. coli with P-plasmid DNA

   b. Identification and isolation of E. coli clones which contain P-plasmid DNA recombinants

   c. Preparation of E. coli cultures containing P-plasmid DNA

3. Inoculation of animals with bacteria containing P-lambda or P-plasmid DNA, with P-lambda phage stocks, or with purified P-lambda or P-plasmid DNAs.

4. Assay of E. coli lysates containing polyoma-λphage for the presence of infectious polyoma virus.

   a. Preparation of bacterial lysates suitable for use in tissue culture systems

   b. Infection of mouse cell tissue cultures with lysates

   c. Purification of progeny polyoma virus

B. P3 Physical Containment

1. Assay of E. coli lysates, demonstrated to be free of viable bacteria, containing polyoma-plasmid recombinant molecules for the presence of infectious polyoma virus.

2. Infection of tissue cultures with purified P-lambda or P-plasmid DNAs (since in these assays polyoma DNA rather than a prokaryotic DNA is the vector).

3. Assay of E. coli lysates, demonstrated to be free of viable bacteria and polyoma lambda phage, for the presence of polyoma polypeptides.

C. P2 Physical Containment

1. In vitro ligation of restriction enzyme cleavage products.

*2. Chemical characterization of purified recombinant DNA subsequent to cloning in bacteria and following phenol deproteinization.

*3. Immunologic assays of polyoma HI antibody present in mouse serum following a 30-minute incubation of the serum at 56-60C.

4. Following the treatment of bacterial lysates containing polyoma-lambda phage with phenol/SDS, the extracts can be handled at the P2 containment level.

VI. PROPOSED MEASURES FOR CONTAINMENT

A. P4

1. All safety practices will be carried out in accordance with the Safety and Operations Manual which is an appendix to this IMUA.

2. The liquid disinfectant to be used at the P4, P3 and P2 levels of containment is a 1:10 dilution of a 4-6% solution of sodium hypochlorite or a 1:10 dilution of clorox or equivalent commercial preparation containing 5.25% sodium hypochlorite (Skulka, A. et al., NARSM #69; Andrew Lewis, Jr., unpublished data).

B. P3

1. All safety practices described under P3 in the Recombinant DNA Research Guidelines (Federal Register 41(131):27913, July 7, 1976) will be adhered to.

2. The choice of disinfectant is stated in VI.A.2.

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*DNA preparations and sera will be tested for sterility prior to their removal from P4 containment. For procedures for testing, see IX. Transfer Of Materials Out Of Class III Cabinets.

3. The pertinent procedures listed under Facility Operations in the P4 Safety and Operations Manual will be adhered to. These include, but are not limited to, change of clothing, showering, out, etc.

C. P2

1. According to practices listed under P2 on Page 27913 of the above issue of the Federal Register.

2. Rooms 218 and 220, Building 5, were previously certified as P1-EK1 under IMUA-10.

D. EK2 Plasmid-Vector System

1. E. coli χ1776 bearing the polyoma-plasmid recombinant should be investigated periodically to ensure that its genotypic and phenotypic properties have not been altered during the course of the experiment.

E. Training

1. The personnel listed on Page One have experience in handling microbial agents equivalent to P2-P3 levels of containment. They will be instructed in the procedures required for the P4 level of containment prior to the commencement of this research. Training and certification of the training will be carried out under the direction of the Project Officer.

VII. MEDICAL SURVEILLANCE PROGRAM

A. Prior to initiation of work each employee shall have:

1. A review of their medical history which should include recent or current antacid or antibiotic therapy.

2. A physical examination.

3. Serum, stool and urine samples taken for storage.

B. Item A3 will be repeated every six months. Stool samples or anal swabs and urine samples will be collected at the discretion of OMS.

C. Medical Coverage

1. The Occupational Medical Service (OMS) will establish a file of all employees participating in this study.

2. Any employee illness must be reported to the OMS. If the employee is unable to report to the OMS directly, he will contact the principal investigator who will notify the OMS.

3. All injuries sustained by employees while working under P4 conditions must be reported to the OMS. These include self-inoculation, aerosol exposures, cuts, abrasions, etc. Appropriate clinical specimens will be collected; serum, urine, stool, throat washing.

4. Workers currently receiving steroids, immunosuppressive drugs or suffering from colitis, ileitis or active/chronic diarrhea will not be permitted to participate in these studies.

5. Any changes in the health status of employees (e.g., peptic ulcer disease, pregnancy) must be reported to OMS. Disposition of employees with these conditions will be determined by OMS policies on these matters.

6. When an employee terminates or the work is completed, a final serum sample will be collected two months later and evaluated for polyoma HI antibodies.

D. OMS has agreed to maintain employee medical records, including a permanent mailing address, for at least 20 years following the cessation of these research activities.

VIII. RADIOISOTOPES

A. Radioisotopes and/or radiolabeled nucleic acids will be used in two separate phases of the P4 experimentation. The regulations described in the Atomic Energy Act of 1954 as published in the Code of Federal Regulations: Title 10, Chapter 1, Parts 19, 20 and 30 will be followed.

1. The principal investigator (Dr. Malcolm Martin) has an NIH license (336) to use radioisotopes. This was granted following the completion of a two-week training course in 1968 and a subsequent one-day refresher session in 1976.

2. Other investigators participating in the work have had training and work experience with radioisotopes. In addition, the investigators will attend a one-day course entitled, "Radiation Safety in the Laboratory" conducted by the Radiation Safety Branch, DRS.

B. Description of the Experimental Use of Radioisotopes

1. Radiolabeled P-lambda or P-plasmid recombinant DNAs will be prepared in appropriate liquid medium with ^{32}P-orthophosphate or ^{3}H-thymidine. Nucleic acids will be removed from the Class III cabinet when it has been demonstrated that such preparations are sterile (see IX(B)1).

2. Fragmented, ^{32}P-labeled polyoma DNA will be used as a probe in the colony hybridization procedure (Grunstein and Hogness, Proc. Nat. Acad. Sci.: U.S.A., 72, 3961-3965, 1975).

C. Quantities of Radioisotopes to be Used

1. ^{32}P-orthophosphate--not to exceed 6 mCi/week.

2. ^{3}H-thymidine--not to exceed 2 mCi/week.

D. Procedures to be Followed

1. Records of incoming radioactive materials and laboratory surveys for radioactive materials will be maintained in the clean area of the Mobile Containment Laboratory (see Page 11 and Section I(4) of the Safety and Operations Manual) in order to permit examination at any time by Radiation Safety Branch personnel.

2. Only working quantities of radioactive materials will be introduced in the Class III cabinet system.

3. Operations with ^{32}P-orthophosphate will be conducted behind lucite shields.

4. Film badges will be placed in heat-sealed polyethylene bags prior to their introduction into the facility and will be taped to the gowns of laboratory personnel. Prior to their removal from the facility the bags will be surface decontaminated in the peracetic acid pass box and then submitted for routine examination.

5. Swabs to detect radioactive contamination in the Class III cabinet will be placed in a leakproof container which will be surface decontaminated. The container and its contents will then be autoclaved prior to removal from the facility. This procedure will then allow for the addition of a scintillation cocktail to the counting vial in a P2 laboratory.

6. Solid and liquid wastes will be separated, decontaminated as described in Section I.2.(C).1, Page 18, of the Safety and Operations Manual, and disposed of by the Radiation Safety Branch in the usual fashion.

IX. TRANSFER OF MATERIALS OUT OF CLASS III CABINETS

A. Potentially Hazardous Material

1. Bacterial cultures containing P-lambda or P-plasmid recombinant DNAs that have been propagated in the Mobile Containment Laboratory will be transferred to Building 550, Frederick Cancer Research Center (FCRC) for inoculation into mice and hamsters. Packaging and transportation of all recombinant DNA materials will be carried out in accordance with the relevant sections of the NIH Guidelines.

2. Such material will be placed in a primary container which will be surface decontaminated. The primary container will then be sealed in a leakproof secondary container in the Class III cabinet.

3. The leakproof container will be transferred out of the cabinet via the dunk tank and surface decontaminated with peracetic acid spray during transit through the pass box.

4. The container will be labeled with the warning: "Open Only Under P4 Containment."

B: Non-Infectious Material for Biochemical Analysis

1. Lysate of bacteria containing P-plasmid DNA recombinant molecules.

   a. Cultures containing P-plasmid recombinant DNA will be shaken with 1% chloroform at room temperature for ten minutes.

   b. One milliliter of the treated culture will be added to L broth containing diamimopimelic acid and thymidine and incubated at 37C for 24 hours.

   c. If the medium remains sterile, the preparations will be removed from the Class III cabinet:

      (i) As described in Section I.2.(C).1, Page 18, of the Safety and Operations Manual for work conducted in the Mobile Containment Laboratory;

      - or -

      (ii) Through a chemical dunk tank and then surface-decontaminated with ethylene oxide gas prior to removal from Building 550, FCRC.

2. Lysates of bacteria containing P-lambda DNA recombinant molecules.

   a. In those cases where P-lambda lysates will be examined for the presence of polyoma-specific RNA or polypeptides, E. coli K12 strain supO (non-suppressor containing host) will be used. Under these conditions, no progeny phage of P-lambda Wam 403 Eam 1100 Sam 100 will be made. The bacterial cultures will be treated with 1% chloroform and assayed for the presence of viable bacteria as described above.

   b. Materials derived from experiments in which λ phage vectors are employed will be tested also for the absence of P-λ phage using E. coli DP-50 supF. Materials can be considered free of P-λ phage if 20µl of the undiluted lysate or serum yield no plaques when plated with E. coli DP-50 supF.

   c. If the L broth remains sterile and no plaques are seen, the preparation will be removed from the Class III cabinet and the P4 facility by procedures described in IX(B)1Ci or IX(B)1Cii above.

3. P-lambda DNA

   a. P-lambda DNA will be prepared from purified P-lambda phage particles by deproteinization with SDS-phenol under P4 conditions.

   b. The bacterial sterility of purified DNA will be assessed by the addition of 10µg of DNA to L broth followed by a 24-hour incubation at 37C.

c. 10µg of DNase-treated DNA will be plated with E. coli DP-50 supF.

d. If the medium remains sterile and no plaques are seen, P-lambda DNA will be removed from the Class III cabinet and the P4 facility by the procedures described in IX(B)1Ci or IX(B)1Cii above.

4. Serum

a. Serum samples will be heated at 60C for 30 minutes.

b. Undiluted samples (0.05 ml) will be added to L broth as described above.

c. If the cultures are sterile, the sera will be removed from the Class III cabinet and Building 550, FCRC, as described in IX(B)1Cii above.

d. A 0.05 ml serum sample derived from animals exposed to P-λ vectors will be plated with E. coli DP-50 supF. If no plaques develop, the serum sample can be considered free of P-λ phage.

STATEMENT OF UNDERSTANDING AND AGREEMENT

We, the signatories below, have read and understood Manual Issuance #3031-1, "Control of Certain Hazardous and Potentially Hazardous Microbiological Agents in Intramural Research," and agree that in the handling and conduct of studies on the controlled agent described above that we will adhere to the procedures and restrictions outlined in the foregoing and will use any additional precautions necessary to contain the agent to prevent human, animal or plant infections.

REQUESTING INVESTIGATORS:

Malcolm A. Martin, M.D.

Hardy Chan, Ph.D.

Mark A. Israel, M.D.

Aurobindo Roy, D.Sc.

LABORATORY CHIEFS:

Wallace P. Rowe, M.D., Chief, Laboratory of Viral Diseases, NIAID
(And Requesting Investigator)

Norman P. Salzman, Ph.D., Chief, Laboratory of Biology of Viruses, NIAID

ACTING SCIENTIFIC DIRECTOR, NIAID:

Franklin A. Neva, M.D.

DEPUTY DIRECTOR, NIAID:

5/23/77

John R. Seal, M.D.

APPROVED: _____

DeWitt Stetten, Jr., M.D., Ph.D. (DATE)
Deputy Director for Science, NIH

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